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Aggressive B-cell lymphomas of sinonasal tract and testis – clinical manifestations and treatment outcome

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1 Original publications

The thesis is based on the following original publications. The publications are referred to in the text by Roman numerals (I-IV):

I. Vähämurto P, Silventoinen K, Vento SI, Karjalainen-Lindsberg ML, Haapaniemi A, Bäck L, Mannisto S, Leppä S, Mäkitie AA. Clinical findings of extranodal SNT lymphoid malignancies in a four-decade single-centre series. Eur Arch Otorhinolaryngol. 2016 Nov;273(11):3839-3845.

II. Vähämurto P, Mannisto S, Pollari M, Karjalainen-Lindsberg ML, Mäkitie AA, Leppä S. Clinical features and outcome of the patients with sinonasal tract diffuse large B-cell lymphoma in the pre-rituximab and rituximab eras. Clinical features and outcome of the patients with sinonasal tract diffuse large B-cell lymphoma in the pre-rituximab and rituximab eras. Eur J Haematol. 2019 Jun;102(6):457-464.

III. Mannisto S, Vähämurto P*, Pollari M*, Clausen MR*, Jyrkkiö S, Kellokumpu-Lehtinen PL, Kovanen P, Karjalainen-Lindsberg ML, d'Amore F, Leppä S. Intravenous but not intrathecal central nervous system-directed chemotherapy improves survival in patients with testicular diffuse large B-cell lymphoma. Eur J Cancer. 2019 May; 10 (115):27-36.**

IV. Vähämurto P, Pollari M, Clausen MR, d'Amore F, Leppä S, Mannisto S. Low blood absolute lymphocyte counts in the peripheral blood predict inferior survival and improves the International Prognostic Index in testicular diffuse large B-cell lymphoma. Cancers 2020, 12(7), 1967

*= equal contribution

**= This publication has also been used in Marjukka Pollari's doctoral thesis

In addition, some unpublished data is shown.

2 Abbreviations

aaIPI	age-adjusted IPI
ABC	activated B-cell (phenotype)
AIDS	acquired immunodeficiency syndrome
AMC	absolute monocyte count (in whole blood)
ALC	absolute lymphocyte count (in whole blood)
ALK	anaplastic lymphoma kinase
AraC	cytarabine
ASCT	autologous stem cell transplantation
B-ALL	B-cell acute lymphocytic leukaemia
B-CLL	B-cell chronic lymphocytic leukaemia
BACOD	bleomycin, adriamycin (doxorubicin), cyclophosphamide, vincristine and dexamethasone
BAIOD	bleomycin, doxorubicin, ifosfamide, vincristine and dexamethasone
BCL2	B-cell lymphoma 2
BCL6	B-cell lymphoma 6
BCR	B-cell receptor
BL	Burkitt lymphoma
B-LBL	B-lymphoblastic leukemia/lymphoma
BTK	bruton tyrosine kinase
CAR-T	chimeric antigen receptor T-cell
CD10	cluster of differentiation 10
CHOP	cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine and prednisone/prednisolone
CHOEP	cyclophosphamide, hydroxydaunorubicin, vincristine, etoposide and prednisone

CNOP	cyclophosphamide, mitoxantrone, vincristine, prednisone
COP	cyclophosphamide, vincristine and prednisone
C(X)OP	cyclophosphamide, unspecified substance, vincristine and prednisone
CNS	central nervous system
CNS dir	CNS directed
COO	cell of origin
CR	complete response
CT	computed tomography
DA-EPOCH-R	dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab
DH	double-hit
DHAP	dexamethasone, high-dose cytarabine, cisplatin
dir	directed
DNA	deoxyribonucleic acid
DLBCL	diffuse large B-cell lymphoma
DPE	double protein expressor
DSS	disease-specific survival
EBV	Epstein Barr virus
ECOG	Eastern Cooperative Oncology Group (performance status)
[^{18}F] FDG	18-fluoro-2-deoxyglycose
FOXP1	forkhead box protein 1 (a transcription factor)
GC	germinal centre
GCB	germinal centre B-cell
GDP	gemcitabine, dexamethasone, cisplatin
HDCT	high-dose chemotherapy

HGBL	high-grade B-cell lymphoma
HHV8	human herpes virus 8
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IFRT	involved-field radiotherapy
ICE	ifosfamide, carboplatin, etoposide
IPI	international prognostic index
it	intra thecal
iv	intra venous
IRF4	interferon regulatory factor 4
Ki67	a cell proliferation marker
LDH	lactate dehydrogenase
LMR	lymphocyte to monocyte ratio
MCL	Mantle cell lymphoma
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTV	metabolic tumour volume
MTX	methotrexate
MUM1	melanoma-associated antigen 1
MYC	*(c-myc)* myelocytomatosis viral oncogene homolog (cancer)
NFkB	nuclear factor kappa B
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
OS	overall survival
p53	protein 53

PAX5	paired box protein 5
PD	progressive disease
PD-1	programmed death 1
PDL-1	programmed death ligand 1
PFS	progression-free survival
PET	positron emission tomography
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	primary testicular
R	rituximab
R-ACVBP	dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone
RT	radiotherapy
SD	stable disease
SNT	sinonasal tract
TH	triple-hit
TMA	tissue microarray
WHO	world health organization

3 Abstract

Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell lymphoma that without treatment rapidly leads to death. Addition of monoclonal CD20 antibody rituximab (R) to cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine and prednisone (CHOP) chemotherapy has clearly improved survival of patients with DLBCL, and now 74% of the patients receiving immunochemotherapy are reported to remain event free in 6-year follow-up. However, extranodal DLBCL, especially primary testicular (PT) DLBCL, primary central nervous system (CNS) DLBCL, renal/adrenal DLBCL, and according to some earlier reports also sinonasal tract (SNT) DLBCL, have worse prognosis than DLBCL in general. In addition, the impact of the addition of R on the survival of specific subgroups, like PT-DLBCL and SNT DLBCL is not clear. In this study the clinicopathological presentation and impact of the addition of R on the survival of the patients with SNT and PT-DLBCL was analysed.

SNT and PT-DLBCL have also been considered to have high risk for CNS spread. To prevent CNS spread, CNS-directed therapy (*iv* high-dose methotrexate or *iv* cytarabine) is added for patients with high risk for CNS spread. However, the significance of CNS-directed chemotherapy on SNT and PT-DLBCL patients is unclear and this study aimed to explore it.

The clinical data and samples of SNT lymphoma patients treated at the Helsinki University Hospital (Helsinki, Finland) and SNT DLBCL patients also from Tampere University Hospital (Tampere, Finland) were collected and the outcomes in response to different treatment modalities were compared.

The present study shows the incidence of SNT lymphoid malignancies is slowly increasing, and that nasopharynx is the most common location in the SNT area. Majority (43%) of the patients had DLBCL, whereas 18% had plasmocytoma.

SNT DLBCL patients receiving R and CNS-directed therapy in addition to CHOP-like therapy had longer survival than patients not receiving these as part of their therapy, and the patients receiving both R and CNS-directed therapy as part of their therapy had the longest survival.

PT-DLBCL patients were chosen here to present another extranodal patient group. Clinical data and samples of PT-DLBCL patients treated at Helsinki, Tampere and Turku University Hospitals were collected, and in addition, Danish lymphoma registry was searched for PT-DLBCL patients.

It was observed that PT-DLBCL patients with high international prognostic index (IPI) clearly benefitted from the addition of R to the treatment and that the treatment of contralateral testis associated with better survival among all PT-DLBCL patients. The present study demonstrates non-GCB phenotype in PT-DLBCL was associated with inferior survival. PT-DLBCL patients treated with *iv* CNS-directed treatment had significantly better survival than other patients.

The present study identified absolute lymphocyte count (ALC) as a potential risk factor in PT-DLBCL. Non-lymphopenic PT-DLBCL patients receiving R as a part of their chemotherapy were found to have better survival in comparison to the patients not receiving R, whereas among lymphopenic patients, the difference in the outcome between the patients receiving R and not receiving R as part of their chemotherapy was not observed. Likewise, non-lymphopenic patients benefitted of *iv* CNS-directed therapy, whereas among lymphopenic patients no clear survival benefit was observed.

4 General introduction

4.1 Immunology

4.1.1 Lymphatic system

Lymphatic system is divided into primary lymphoid organs (bone marrow and thymus), secondary lymphoid organs (like spleen and lymph nodes) and tertiary lymphoid organs, which refers to practically any tissues where lymphocytes migrate and accumulate in infection. The development of lymphocytes takes place in primary lymphoid organs, whereas antigen presentation, somatic hypermutation and class switch recombination take place in secondary lymphoid organs. Antigen presenting cells (like dendritic cells or macrophages) process antigens, bind them to major histocompatibility complex (MHC) and present them on their cell-surface for lymphocytes.

Lymphocytes monitor for foreign antigens, which antigen presenting cells present for them in the lymph nodes. Lymphocytes circulate in blood, exit circulation in peripheric capillaries and via lymphatic vessels end up in lymph nodes. Lymphocytes enter circulation again with lymph via thoracic duct.

Primary lymphoid organs

Secondary lymphoid organs

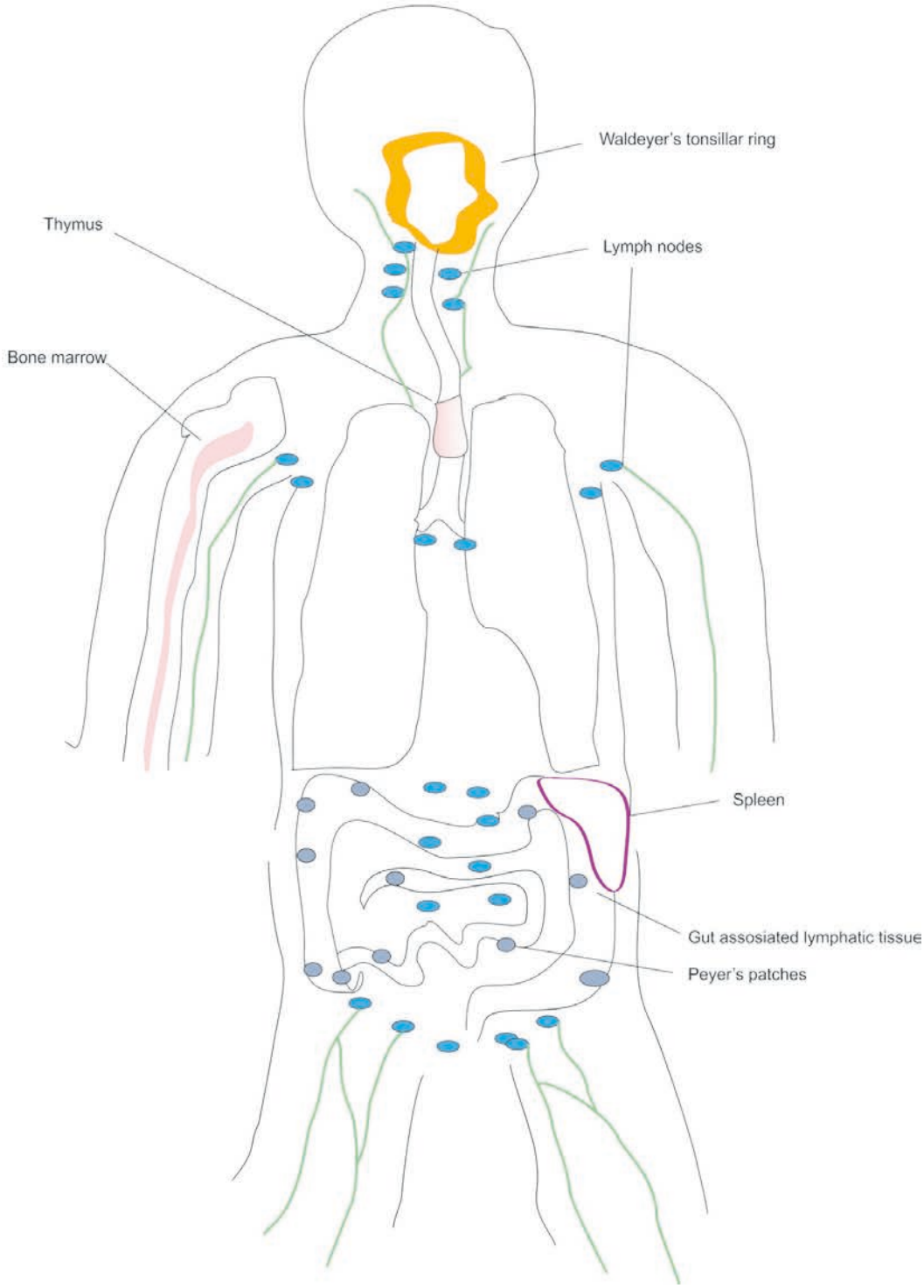

Figure 4.1 Schematic illustration of lymphatic system; lymphatic stem cells develop to pro B-cells, pro T-cells and T/NK stem cells in bone marrow. Pro B-cells develop in bone marrow further to immature B-cells and enter circulation as naïve B-cells. Pro T-cells migrate to thymus for development through cortical and medullar T-cells to cluster of differentiation (CD) 4+ and CD 8+ T-cells. Only a few lymphatic vessels shown in the figure (in green).

4.1.2 Natural barriers, innate and adaptive immunity

Pathogens that have overcome the outer barriers of human body, like skin or mucosa, are confronted by immune system, which is comprised of innate and adaptive immunity.

Innate immunity is comprised of several components; the aforementioned outer barrier, complement that is activated for instance by foreign bodies and pathogens or damaged cells, cytokines that recruit immune cells to infection site and leukocytes of innate immunity; mast cells, eosinophils, basophils, natural killer cells and phagocytic cells; macrophages, neutrophils and dendritic cells. Innate immunity also activates adaptive immunity through antigen presentation.

Adaptive immunity comprises B- and T- lymphocytes, i.e. B- and T-cells. These cells recognize foreign bodies with antigen specific antibodies.

4.1.3 B-cell maturation

Hematopoietic stem cells develop to stem cells of myeloid and lymphoid lineage in bone marrow (Figure 4.1). Naïve B-cells produced in bone marrow migrate from bone marrow to secondary lymphoid organs, where they encounter their antigen. B-cells are activated in interaction with antigen presenting cells, like dendritic cells, and form germinal centres (GC). In somatic hypermutation, taking place in GS (Figure 4.2), point mutations take place in the variable region of immunoglobulin genes in B-cells leading to B-cells with higher affinity for the foreign substance. In class switch recombination the B-cells undergo class switching, in which the variable region remains the same but antibody class is changed, to produce IgG, IgA and IgE antibodies.

After this process, B-cells become plasma cells and memory B-cells. If the same antibody is encountered later in life, the memory B-cells become activated and cause faster, stronger and more precise immune response.

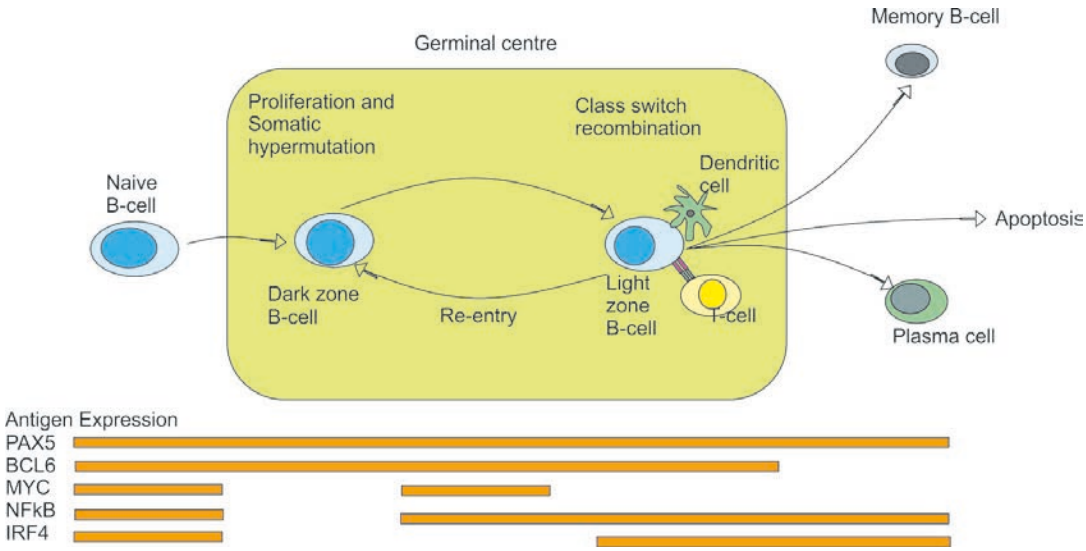

Figure 4.2 Maturation of B-cell. B-cells undergo somatic hypermutation and class switch recombination in germinal centre. This process forms B-cells with high affinity receptors for the foreign antigen they have faced. The clones of B-cells with highest affinity receptors survive, while others undergo apoptosis. Some of the B-cells become plasma cells and produce antibodies targeted for the foreign antigen, while others become memory B-cells (modified from Basso, Dalla-Favera 2015, Pasqualucci, Zhang 2016, Pasqualucci 2019)

As summarized by Basso & Dalla-Favera 2015 and Pasqualucci & Dalla-Favera 2015, GC has two distinct zones, light zone and dark zone. B-cells cycle between these two zones during their maturation process. A number of transcription factors are needed in the GC initiation and exit, and malfunctioning of these same pathways is involved in lymphomagenesis. During GC initiation, *NFkB* and *IRF4* are expressed, leading to *BCL6* induction and GC formation. Expression of *MYC* is required in GC formation and for B-cells to re-enter to dark zone, but BCL6 silences the expression in dark zone. BCL6 is crucial in somatic hypermutation, as it inhibits cell cycle arrest and apoptosis making B-cells more tolerant for DNA-damage and allowing more DNA remodeling, while malfunctioning and constantly active BCL6 expression thrives lymphomagenesis (Pasqualucci, Dalla-Favera 2015, Swerdlow et al., 2017).

CD20 is expressed at almost all stages of B-cell development, except for very early stage B-cells, pre-pro-B-cells, and mature plasma cells (Stashenko et al., 1980, Glennie et al., 2007). There is no known ligand of CD20, yet it is important in B-cell signaling and differentiation (Beers et al., 2010, Uchida et al., 2004).

5 Aggressive B-cell lymphomas

5.1 Background

History of lymphoma research can be considered to have begun at the time of description of Hodgkin's disease/lymphoma 1832. Already in early 1900s radiotherapy yielded transient treatment results in lymphomas and in 1920s and 30s a more systematic approach was reached (Aisenberg 2000). However, during last eight decades, our understanding of lymphomas and hematologic malignancies has increased dramatically. AIDS (acquired immunodeficiency syndrome) related lymphomas increased the incidence of lymphomas in 1980s and 1990s (Aisenberg 2000, Fisher, Fisher 2004). Cyclophosphamide, hydroxydaunorubicine (doxorubicin), vincristine and prednisone (CHOP) treatment was introduced already in the 1970s for intermediate and high-grade lymphomas (Aisenberg 2000, McKelvey et al., 1976, The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993). Since the 90s, CHOP has been the backbone for treatment of DLBCL (Fisher et al., 1994, Cooper et al., 1994, Gordon et al., 1992). Introduction of monoclonal CD20 antibody rituximab (R) and the addition of R to CHOP chemotherapy started a new era in DLBCL treatment at the turn of the millennium (Feugier et al., 2004, Coiffier et al., 2002, Coiffier et al., 2010, Habermann et al., 2006, Cunningham et al., 2013, Delarue et al., 2013, Pfreundschuh et al., 2008, Pfreundschuh et al., 2006).

Lymphomas are group of diverse diseases, historically divided to Hodgkin's and non-Hodgkin lymphomas (NHL). The incidence of lymphomas has been increasing in Western countries during the last decades, which has been considered to result from better diagnostics and reporting, amount of lymphomas induced by AIDS and increase in the number of elderly population (Aisenberg 2000, Fisher, Fisher 2004, Martelli et al., 2013). Immune system is at weakest during the first years of life and at old age, which along with through life accumulating mutations explains higher incidence of lymphomas in elderly population (Fisher, Fisher 2004, Martelli et al., 2013).

As summarized by Fisher & Fisher 2004 and Martelli et al. 2013, factors known to predispose for lymphomas are chronic inflammation, immunosuppressive medication, other immunocompromised conditions, alkylating agents (used in oncological treatments), ionic irradiation, consistent antigen stimulation and certain viruses, like hepatitis C. In addition, there are certain lymphoma families with hereditary predisposition to develop lymphomas. However, most patients with lymphoma do not have a clear predisposition for any known precipitating factor.

5.2 Pathogenesis

B- and T-cell malignancies arise from different stages of normal B- and T-cell development and thereby reflect the characteristics of the cell of origin. The basis for classification of malignancies is the equivalent normal

cell of B- or T-cell maturation. However, as not all malignancies have clear normal counterpart, the normal maturation process is not the only basis in the classification.

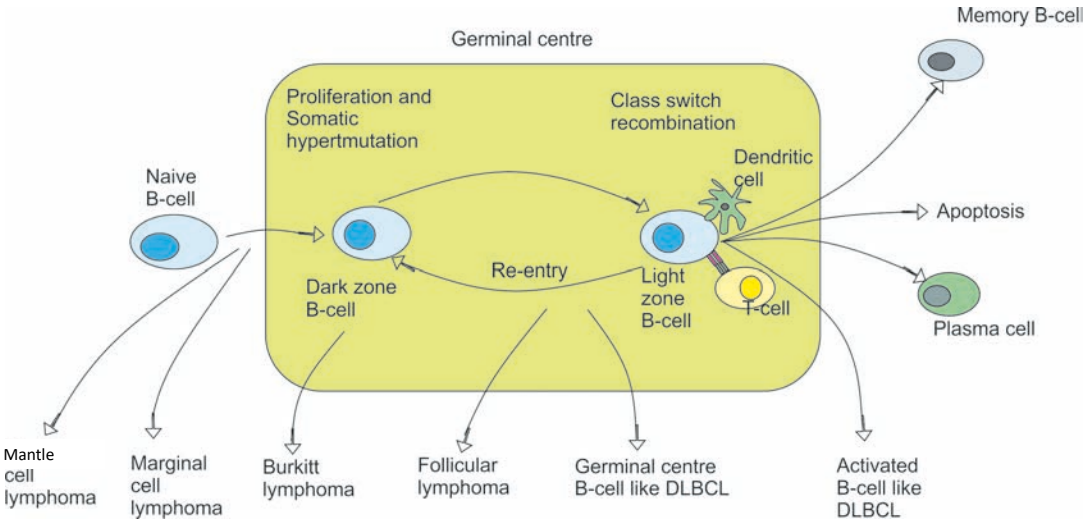

Figure 5.1 Development of mature B-cell lymphomas (modified from Basso, Dalla-Favera 2015, Pasqualucci, Zhang 2016, Rickert 2013)

Even in normal maturation process of B-cells, somatic hypermutation and class switch recombination produce substantial amount of mutations and variance. However, the large amount of mutations can lead to cease in B-cell maturation and unlimitedly replicating cell-clone, i.e. lymphoid malignancy (Basso, Dalla-Favera 2015, Rickert 2013). Indeed, the B-cell lymphomas reflect different developmental stages of B-cell lifecycle, but the majority is derived from antigen-experienced GC or post GC B-cells (Basso, Dalla-Favera 2015, Young, Staudt 2013). The importance of GC in the formation of lymphomas has been shown in mice. In a mouse model prone for lymphomas the deletion of an enzyme required for somatic hypermutation and class switch recombination, prevented the development of GC-derived lymphomas (Pasqualucci, Dalla-Favera 2018).

B-cell malignancies reflect in their gene-expression B-cells at different stages of B-cell development. B-cell acute lymphocytic leukemia (B-ALL) is derived from pre-B-cells in bone marrow, whereas B-cell chronic lymphocytic leukemia (B-CLL) and mantle cell lymphoma (MCL) are derived from circulating B-cells (Swerdlow et al., 2017, Rickert 2013, Young, Staudt 2013). The majority of B-cell malignancies arise from germinal centre B-cells; Burkitt lymphomas derive from dark zone GC cells, whereas follicular lymphomas and germinal centre like B-cell (GCB) DLBCL derive from B-cells arrested at different stages of GC events (Basso, Dalla-Favera 2015, Swerdlow et al., 2017, Rickert 2013, Alizadeh et al., 2000). Activated B-cell like

(ABC) DLBCL on the contrary derives from B-cells arrested early in post-GC differentiation and committed already to plasmablastic differentiation (Basso, Dalla-Favera 2015, Swerdlow et al., 2017, Alizadeh et al., 2000). Primary mediastinal B-cell lymphoma (PMBCL) derives from post-GC thymic B-cells in mediastinum (Basso, Dalla-Favera 2015, Young, Staudt 2013).

5.3 Classification

The latest version of World Health Organization (WHO) classification of the lymphoid neoplasms was published 2017 (Swerdlow et al., 2017). The classification reflects a consensus among the experts of their own field; hematopathologists, geneticists and clinicians. The classification describes over 90 different entities. The classification divides mature aggressive B-cell malignancies to entities described in Table 5.1, according to morphological, biological and clinical differences, but this thesis will concentrate on the most common one, DLBCL not otherwise specified (NOS). High grade B-cell lymphoma (HGBL) is also presented more in detail, to clarify the difference of double-hit (DH) lymphoma and double protein expressor (DPE) DLBCL.

The majority of DLBCL cases belong in DLBCL NOS -category (Swerdlow et al., 2017). Primary mediastinal B-cell lymphoma (PMBCL) and primary diffuse large B-cell lymphoma of CNS for instance are molecularly distinct entities and thus different from DLBCL NOS (Swerdlow et al., 2017, Martelli et al., 2017). Primary testicular DLBCL (PT-DLBCL) is also suggested as an own entity, separate from nodal ABC-DLBCL, as it is shown to share numerous genetic alterations with primary CNS lymphoma and to have genetic signature different from DLBCL NOS (Twa et al., 2018, Deng et al., 2016, Chapuy et al., 2016, Ollila, Olszewski 2018). Still, in the revised WHO classification PT-DLBCL is not considered as a distinct entity.

Table 5.1 Aggressive mature B-cell neoplasms, classification, *=provisional entity (modified from Swerdlow et al., 2017)

Aggressive mature B-cell neoplasms		
Diffuse large B-cell lymphoma, NOS		
	Morphologic variants	
		Centroblastic
		Immunoblastic
		Anaplastic
		Other rare variants
	Molecular subtypes	
		Germinal centre B-cell subtype
		Activated B-cell subtype
Other lymphomas of large B-cells		
	T-cell/histiocyte-rich large B-cell lymphoma	
	Primary diffuse large B-cell lymphoma of the CNS	
	Primary cutaneous diffuse large B-cell lymphoma, leg type	
	EBV-positive diffuse large B-cell lymphoma, NOS	
	Diffuse large B-cell lymphoma associated with chronic inflammation	
	Lymphomatoid granulomatosis	
	Large B-cell lymphoma with *IRF4* rearrangement	
	Primary mediastinal (thymic) large B-cell lymphoma	
	Intravascular large B-cell lymphoma	
	ALK-positive large B-cell lymphoma	
	Plasmablastic lymphoma	
	HHV8-positive diffuse large B-cell lymphoma*	
	Primary effusion lymphoma	
High-grade B-cell lymphoma		
	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement	
	High-grade B-cell lymphoma, NOS	
B-cell lymphoma, unclassifiable		
	B-cell lymphoma, unclassifiable, with features intermediate between Diffuse large B-cell lymphoma and classic Hodgkin's lymphoma	

5.4 High-grade lymphomas

According to the updated world health organization (WHO) classification, high-grade B-cell lymphomas (HGBL) with MYC and BCL2 and/or BCL6 rearrangement are considered as their own entity (Swerdlow et al., 2017). These double-hit (DH) and triple-hit (TH) lymphomas are more aggressive lymphomas and have inferior survival than DLBCL without these gene-rearrangements (Swerdlow et al., 2017, Sarkozy et al., 2015, Akyurek et al., 2012). HGBLs have mutational profile intermediate between Burkitt lymphoma and DLBCL, and a clearly worse outcome (Swerdlow et al., 2017, Sarkozy et al., 2015, Akyurek et al., 2012, Johnson et al., 2012). (More of genetics in section 5.5.5 Genetics and immunophenotype)

The updated WHO classification recognizes also HGBL NOS. This category includes lymphomas that have high grade morphology, but lack the aforementioned rearrangements (Swerdlow et al., 2017). As HGBLs have dismal outcome, and are potentially treated with different treatment approach, they are important to be recognized.

Double protein expressor (DPE) DLBCL refers to lymphoma with high expression of MYC and BCL2 or BCL6, and triple protein expressor DLBCL to lymphoma with high expression of MYC and BCL2 and BCL6. This does not, however, mean the disease would necessarily be HGBL, but nonetheless, DPE has been recognized as an adverse prognostic factor. (Sarkozy et al., 2015, Johnson et al., 2012)

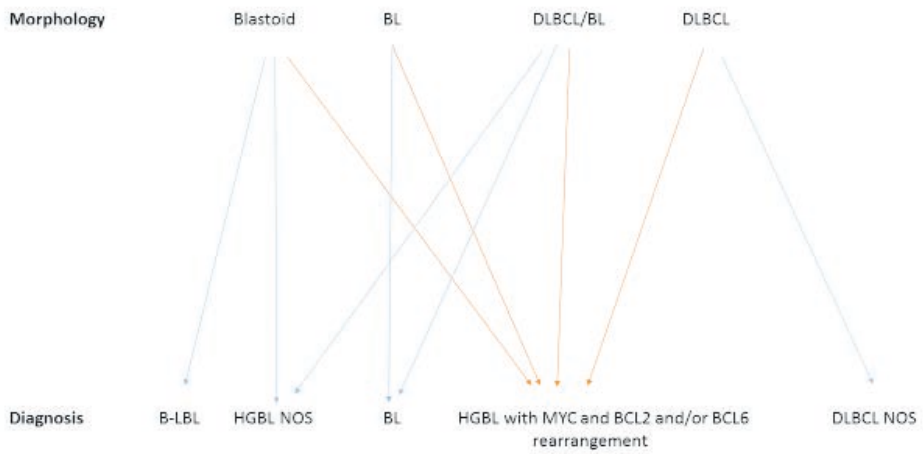

Figure 5.2 Updated classification of high-grade B-cell lymphomas; Burkitt Lymphoma (BL), Diffuse Large B-cell lymphoma (DLBCL), B-lymphoblastic leukemia/lymphoma (B-LBL), high-grade B-cell lymphoma (HGBCL). The cases with MYC and BCL2 and/or BCL6 rearrangement are illustrated with orange arrows (modified from Swerdlow et al., 2017)

5.5 DLBCL NOS

5.5.1 Epidemiology

Incidence for Diffuse large B-cell lymphoma (DLBCL) per 100 000 is 13.24 for men and 9.34 for women in Finland (2013-2017 data, web page of Finnish Cancer Registry, www.syoparekisteri.fi). Approximately 1800 mature B-cell lymphomas are diagnosed in Finland annually, and one third of these are DLBCLs (data of year 2016) (Leppä et al., 2019). The median age for DLBCL patients at diagnosis is 60-70 (Martelli et al., 2013). Today, over half of the patients can be cured (Leppä et al., 2019). In Finland, the overall survival for patients under 65 years at diagnosis is 75%, whereas 46% of patients over 65 years at diagnosis are alive after 5 years (Leppä et al., 2019).

5.5.2 Diagnostics

When a patient is suspected to have a lymphoma based on his/her symptoms, a representative tissue sample of affected lymph node or extranodal manifestation should be attained. The biopsies of suspected lymphoma patients should be evaluated by a hematopathologist. In addition, blood samples are taken (like LDH and blood cell counts) and human immunodeficiency virus (HIV) positivity/negativity is defined. Patient-related clinical factors, like Eastern Cooperative Oncology Group (ECOG) performance status, are recorded. The stage of the disease is defined (see 5.6.1 Staging). The international prognostic index (IPI) is defined according to its factors (see 5.5.7 Prognostic factors). (Tilly et al., 2015, Cheson et al., 2014, Cheson et al., 2007)

5.5.3 Morphology

DLBCL is a malignancy of large B-cells with nucleus size equal to or larger than nucleus of a normal macrophage or greater than twice the size of a normal lymphocyte and that have diffuse growth pattern, (Figure 5.3). DLBCL has three common morphological variants; centroblastic, immunoblastic and anaplastic, and in addition more rare morphological variants (Swerdlow et al., 2017).

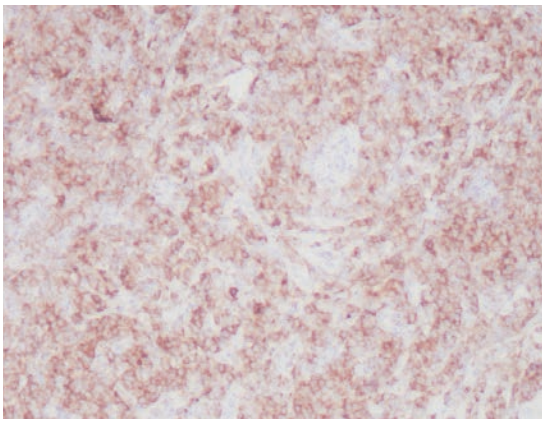

Figure 5.3 CD10 positive SNT DLBCL

5.5.4 Molecular subtype

Gene expression profiling (GEP) based classification divides DLBCL NOS molecularly to germinal centre B-cell (GCB), activated B-cell (ABC), with ABC type having inferior survival compared to GCB, and unclassified subtype (Swerdlow et al., 2017, Alizadeh et al., 2000, Lenz et al., 2008). The GCB subtype has a gene expression profile similar to germinal centre (GC) B-cells whereas cells with ABC-like expression profile have GEP similar to activated B-cells (Alizadeh et al., 2000). In addition, unclassifiable group or type 3 group has also been described (Alizadeh et al., 2000, Wright et al., 2003, Rosenwald et al., 2002).

5.5.5 Immunohistochemical algorithms

Immunohistochemical algorithms have been incorporated into clinical practice, as GEP-based classification is not yet available in routine clinical practice at most institutions. Widely used Hans algorithm (Figure 5.4) divides DLBCL to GCB and non-GCB subtypes (Hans et al., 2004). In Hans algorithm, molecular markers clearly associated with either GCB or non-GCB subgroups in the GEP-based studies, are analyzed with immunohistochemistry; CD10, BCL6 and MUM1 (Hans et al., 2004). Nonetheless, Hans algorithm misclassifies approximately 20% of the DLBCL cases, so it cannot be directly compared to GEP-based classification (Hans et al., 2004, Nyman et al., 2007, Seki et al., 2009).

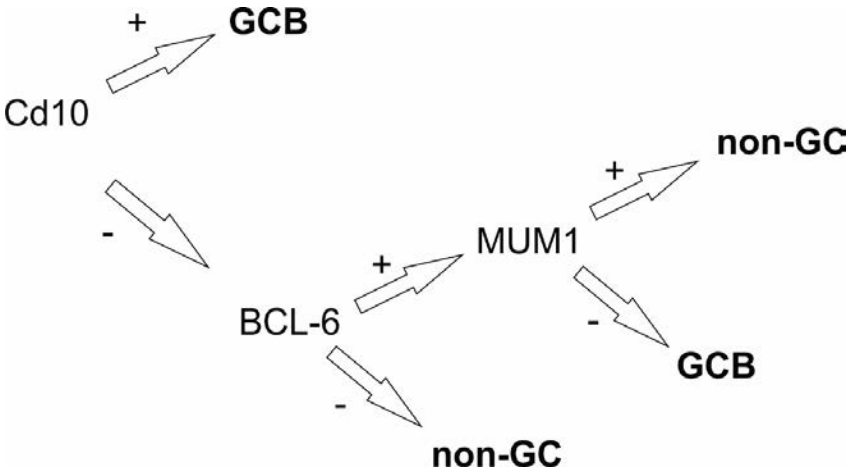

Figure 5.4 Schematic illustration of Hans algorithm (modified from Hans et al., 2004)

5.5.6 Genetics and immunophenotype

DLBCL typically expresses pan-B-cell markers, like CD19, CD20, CD22, CD79a and PAX5, but not necessarily all of them (Pasqualucci 2019, Swerdlow et al., 2017). Antigens like Forkhead box protein 1 (FOXP1), CD10, CD58, B2M, BCL6, BCL2 and MYC are variably expressed (Martelli et al., 2013, Pasqualucci 2013, Reddy et al., 2017).

In over half of DLBCL cases there are aberrant somatic hypermutations in genes that contribute to tumorigenesis, like *MYC* or paired box 5 (*PAX5)* (Pasqualucci 2019, Martelli et al., 2013). In about 35% of DLBCL cases, although with higher frequencies in ABC-DLBCL, genetic aberrations are seen causing rearrangement of *BCL6*, a transcriptional repressor normally expressed in GC B-cells, allowing the activity of *BCL6* even in post-GC B-cells (Pasqualucci 2013, Iqbal et al., 2006, Ye et al., 1993).

Rearrangements of *BCL2*, that supports cellular survival, are also frequent (Pasqualucci, Dalla-Favera 2015, Swerdlow et al., 2017, Miao et al., 2019). Less frequently is seen inactivation of *p53*-gene (Pasqualucci 2013). Still, inactivation of acetyltransferases can cause epigenetic modifications leading to inactivation of p53 (Pasqualucci et al., 2011). Expression of proapoptotic protein p53 is repressed by BCL6 in GC to permit somatic hypermutation and class switch recombination to happen. However, constitutive upregulation of BCL6 leads to inactivation of p53 and thus aids lymphomagenesis (Martelli et al., 2013, Phan, Dalla-Favera 2004).

About 10-14% of GCB DLBCL cases have *MYC* translocation and 35-45% *BCL2* (Pasqualucci, Dalla-Favera 2015, Swerdlow et al., 2017). Indeed, the co-existence of *MYC* and *BCL2* (or less frequently, *BCL6*), is only seen in GCB (Pasqualucci 2019, Swerdlow et al., 2017).

Constitutive activation of NF-kB pathway is typical for ABC-DLBCL. It is caused for instance by mutations in MYD88, CD79A and CD79B (Pasqualucci 2013). The resulting sustained activation of B-cell receptor (BCR) signaling activates multiple pathways, like NF-κB -pathway, that consequently leads to escalation in transcription of survival promoting genes, like BCL2, and inhibitors of apoptosis, and antagonizes p53 thus reducing pro-apoptotic action of p53 (Pasqualucci, Zhang 2016, Swerdlow et al., 2017, Pasqualucci, Dalla-Favera 2018, Pasqualucci 2013, Miao et al., 2019). ABC-DLBCL appears to be dependent on NF-kB activation, as in *in vitro* models inhibition of NF-kB activation leads to cell death in ABC-DLBCL (Basso, Dalla-Favera 2015, Young, Staudt 2013, Pasqualucci 2013).

In addition to morphologic and the presented molecular division, more specific genetic division for DLBCL is emerging. Schmitz et al. found four different genetic subtypes of DLBCL with different phenotype and response to immunochemotherapy (Schmitz et al., 2018).

Chapuy et al. on the other hand, reported about five different subsets based on their genetic analysis of 304 DLBCL cases (Chapuy et al., 2018). They could discriminate a low risk ABC-DLBCL and divide GCB-DLBCL into two with different outcomes. They also identified that the genetic bases of BCL2 and MYC deregulation is large, and thus postulated the current description of HG lymphomas is not precise enough.

Even 60% of DLBCL are lacking normal human leukocyte antigen (HLA) class I -complex on their cell surface, that is necessary for the recognition of tumour-cell by immune-cells. This is the result of inactivating mutations in β2-microglobulin -gene, encoding a subunit of HLA-I, or aberrant expression of HLA-I (Challa-Malladi et al., 2011). Also reduced expression of MHC II has been reported in 40-50% of DLBCL, correlating with poor outcome (Rosenwald et al., 2002, Rimsza et al., 2004).

All in all, the variability of DLBCL coding genome is larger than in other B cell malignancies (Pasqualucci 2013). The increasing data of DLBCL genetics and signaling pathways has led to better understanding of the heterogeneity of DLBCL and revealed vulnerabilities in DLBCL. With more precise stratification of the disease we might be able to target treatments better for patients according to the subgroup of their disease, first in clinical trials and later in every day practice. Emerging novel therapies are introduced in section 5.5.13 Novel therapies

5.5.7 Staging

Staging describes the extent and location(s) of the disease, it enables comparison of patients and standardizes the criteria for the extent of the disease in different studies and provides information of prognosis. After treatment the extent of the disease can be compared to the stage prior to treatment in order to define the response. (Cheson et al., 2014, Cheson et al., 2007) See Table 5.2 for Ann Arbor classification stage.

Table 5.2 Ann Arbor -classification (modified from Cheson et al., 2014), tonsils, Waldeyer's ring and spleen are considered as nodal tissue

Stage	
I	Single lymphatic region involved or a single extranodal location with possible involvement of adjacent lymphatic region
II	Two or more lymphatic regions involved on the same side of the diaphragm or extranodal involvement with lymphatic regions on the same side of diaphragm
III	Lymphatic regions on both sides of the diaphragm involved
IV	Diffuse extranodal involvement with or without lymphatic regions
E	extranodal involvement (for Stages I-II)
B	B-symptoms; fewer, weight loss and night sweat

According to Lugano criteria, 18-fluoro-2-deoxyglycose ([^{18}F] FDG) positron emission tomography (PET) and computed tomography (CT) with contrast agent are recommended for staging for FDG-avid lymphomas (Cheson et al., 2014). Aggressive lymphomas have high glucose metabolism, enabling determination of the extent of the disease with FDG-PET imaging (an example of FDG-PET-CT image in Figure 5.5) (Valls et al., 2016). Even though introduction of FDG-PET into staging has raised a question of Stage migration as compared to historical controls, FDG-PET is recommended and preferred as it makes response evaluation more accurate. (Cheson et al., 2014) Approximately 97% of DLBCL cases are hypermetabolic in FDG-PET-CT (Valls et al., 2016).

In FDG-PET-CT, sites with uptake of FDG in concordance with CT-lesions are considered as positive for lymphoma. On the other hand, FDG-PET-CT can also be used to find the best suitable site for biopsy. When staging with CT, six largest nodes or lymphoma lesions from different representative areas of the body should be measured in two diameters, including possible mediastinal and/or retroperitoneal lesions. An unexplained node enlargement is considered as positive finding. A measurable lymph node is considered to be greater than 1.5cm in largest diameter, whereas a measurable extranodal lesion to be more than 1cm in largest diameter. Smaller lesions are considered and followed as nonmeasured disease. (Tilly et al., 2015, Cheson et al., 2014, Cheson et al., 2007) An example of lymphoma in body-CT in Figure 5.6

The Lugano classification recommends measuring and recording of the longest diameter of a potential bulky disease. Even though no validated clear cut-off value for bulky disease is determined for DLBCL, a diameter of 6-10cm is considered as bulky in DLBCL. (Cheson et al., 2014)

The Lugano classification recommends diameter of 13cm as cutoff for splenomegaly (Cheson et al., 2014). Still, the best determinator for splenic involvement is FDG-PET-CT, as a normal size spleen can be infiltrated

by lymphoma and possible to be detected with FDG-PET-CT. Similar to spleen, an increase in FDG uptake in liver in general or focally supports involvement of liver. FDG-PET-CT is also highly sensitive for bone marrow involvement, and in addition to FDG-PET-CT, a bone marrow biopsy is not required. If detection of a discordant bone marrow histology is important, bone-marrow biopsy might be necessary, or if required in clinical trials. (Cheson et al., 2014)

Distinct criteria for baseline evaluation and response are incorporated for primary CNS lymphoma (Abrey et al., 2005) and extranodal marginal zone lymphomas of mucosa associated lymphoid tissue (MALT) (Zucca et al., 2013).

For patients with suspected CNS involvement, i.e. neurological symptoms, MRI of the head should be done, and also cerebrospinal fluid sample should be taken (Tilly et al., 2015). Example of lymphoma in CNS in Figures 5.7-5.8.

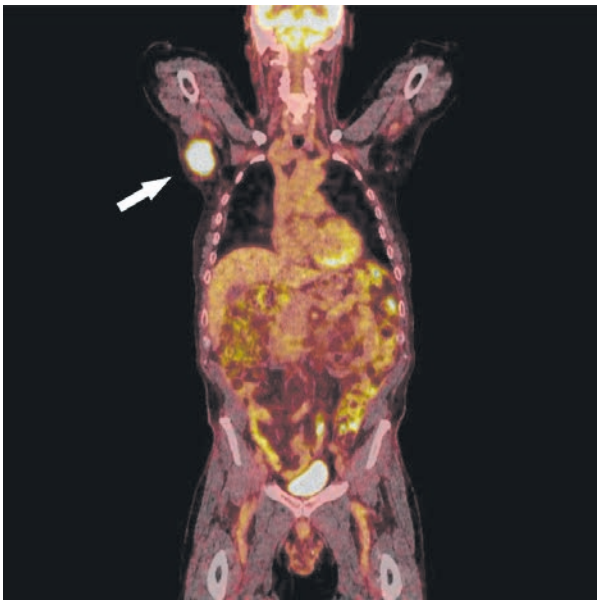

Figure 5.5 FDG-PET-CT of a DLBCL patient, pathological glucose accumulation in right armpit (arrow)

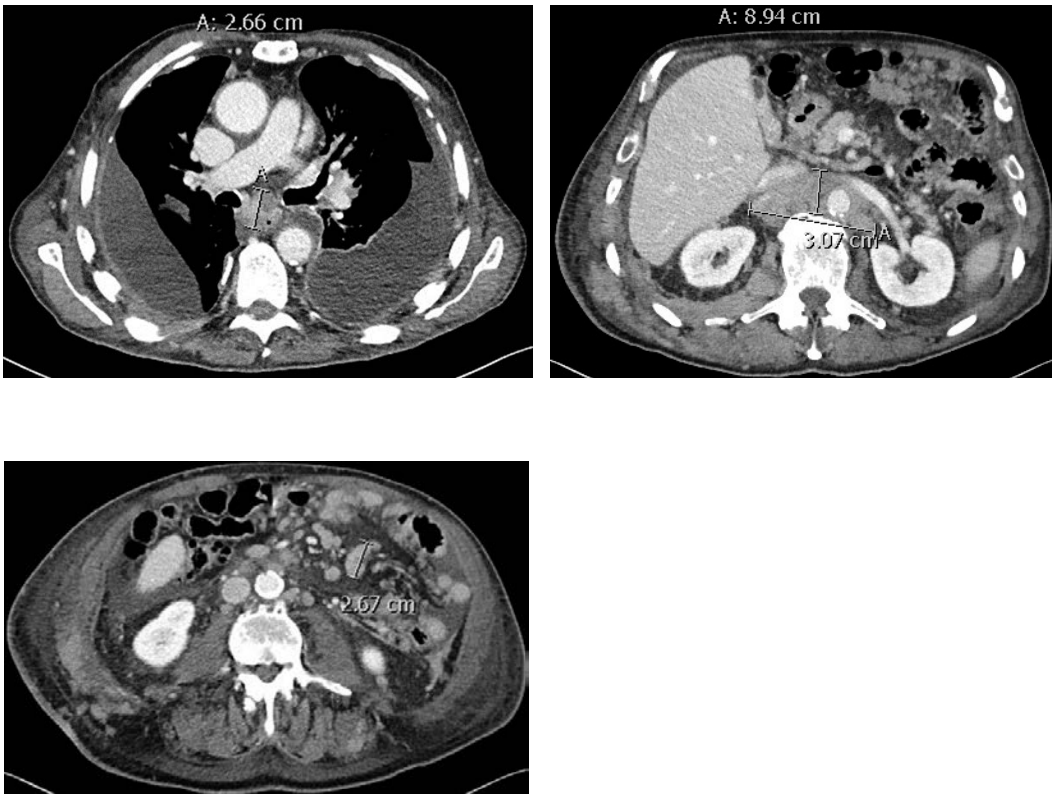

Figure 5.6 Body-CT of a patient with DLBCL, tumour infiltration in mediastinum, para-aortic space and mesenteric lymphadenopathy (measurements) and ascites, in addition pleural enhancement and pleural effusion indicating pleural involvement

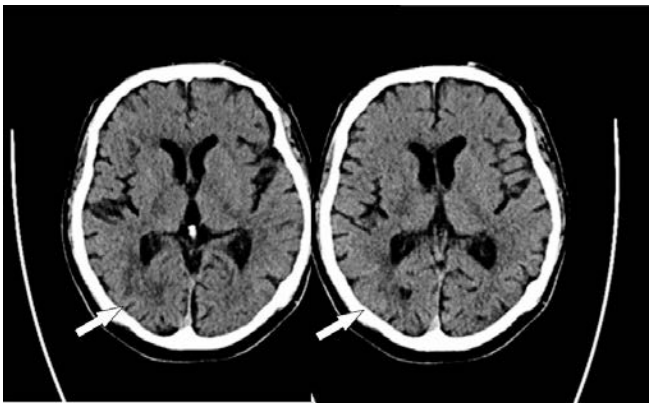

Figure 5.7 CT, tumour infiltration in right occipital lobe (arrow) that later was confirmed as DLBCL

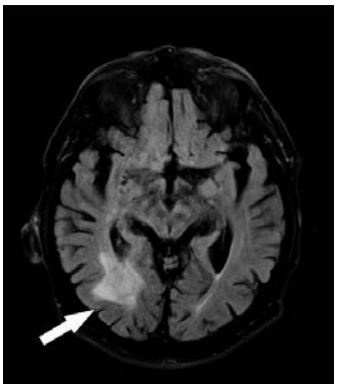

Figure 5.8 MRI, tumour infiltration in right occipital lobe (arrow) that later was confirmed as DLBCL (same patient as in Figure 5.7)

5.5.8 Prognostic factors

5.5.8.1 Clinical prognostic factors

The International prognostic index (IPI) was developed to predict long term survival of non-Hodgkin's lymphoma patients better than merely Ann Arbor Stage does (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993) (See Table 5.2 for Ann Arbor classification stage.) Number of clinical prognostic factors had been recognized before IPI was developed. These factors were evaluated in 2031 patients of all ages. As a result, age over 60y, elevated serum lactate dehydrogenase (LDH), Stage III-IV, ECOG performance status 2-4 and over one extranodal locations were recognized as significant risk factors (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993). See Table 5.3 for ECOG.

Table 5.3 ECOG Performance status (modified from Oken et al., 1982)

Grade	ECOG performance status
0	Performance as prior to the disease
1	Able to carry on light tasks or office work, but restriction in physically burdensome activity
2	Ambulatory patient, capable of taking care of himself, but unable to go on working, active over 50% of waking hours
3	Only limited selfcare is possible, in bed or chair over 50% of waking hours
4	Totally confined to bed or chair
5	Dead

Sehn et al. suggested a revised IPI (R-IPI) for patients treated with immunochemotherapy, dividing the patients into three risk categories (Sehn et al., 2007). However, IPI has proven its prognostic power also for patients receiving immunochemotherapy (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993, Ziepert et al., 2010) (Table 5.4). In the original IPI-study, in analysis of patients under or 60 years of age, stage III-IV, elevated LDH and ECOG performance status 2-4 were recognized as risk factors, which thus constitute the age-adjusted IPI (aaIPI). In clinical practice aaIPI is used commonly to analyze separately patients ≤60 years of age and patients >60 years of age.

Table 5.4 Prognosis according to risk category, estimated survival reported for patients receiving immunochemotherapy (modified from The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993, Ziepert et al., 2010)

Number of risk factors	Risk category	Estimated 3-year overall survival (%)
0-1	low	91
2	low intermediate	81
3	high intermediate	65
4-5	high	59

Zhou et al. reported National Comprehensive Cancer Network IPI (NCCN-IPI), which categorizes the patients receiving immunochemotherapy more precisely to different risk categories, by more detailed categorization of age and LDH (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993, Zhou et al., 2014). Also, only bone marrow, CNS, liver/gastrointestinal tract or lung, were considered as extranodal locations. Zhou et al. reported NCCN-IPI to better recognize patients at high risk and low risk (5y OS in high risk group 33% and in low risk group 96%) than IPI (5y OS for patients in high risk group 54% and low risk group 90%).

Nonetheless, as only clinical prognostic factors constitute IPI, even DLBCL is biologically heterogenous disease, even in low risk category there are patients who relapse within 3 years (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993, Ziepert et al., 2010). Thus, many refinements have been proposed to IPI, but none of these "new IPIs" have clearly replaced the original IPI.

IPI has also been recognized to predict CNS recurrence (Feugier et al., 2004). Furthermore, Schmitz et al. reported in their study on 1597 immunochemotherapy treated patients, of CNS-IPI, that they had developed by studying various potential clinical risk factors for CNS spread (Schmitz et al., 2016). In addition to IPI-factors, their model recognized kidneys and/or adrenal glands as risk factors for CNS spread. They reported the 12% of patients that their model recognized as high risk patients for CNS disease, had 10.2% risk of CNS spread. However, Schmitz et al. could not evaluate the CNS relapse risk for patients with skin involvement, and on the other hand, in their validation set, testicular involvement was a risk factor for CNS recurrence. In their original study set, patients with testicular involvement commonly received *it* MTX, whereas in the validation set, only 10% (Schmitz et al., 2016).

The role of metabolic tumour volume (MTV) in 18-fluoro-2-deoxyglycose ([^{18}F] FDG) positron emission tomography (PET) for predicting outcome in DLBCL is not clear, as there are reports postulating MTV has prognostic value and others not finding an association (reviewed by El-Galaly et al., 2018).

FDG-PET has been reported to be more accurate than CT or MRI in distinguishing residual tumour after therapy, and FDG-PET after immunochemotherapy has predictive value for PFS (Juweid 2011, Coughlan, Elstrom 2014, Pregno et al., 2012). Positive FDG-PET scan during therapy has also been proposed to predict high risk of relapse, but as a positive scan during therapy is not able to identify patients with a worse prognosis, PET positivity during therapy requires histological confirmation (Pregno et al., 2012, Moskowitz et al., 2010, Safar et al., 2012, Tokola et al., 2020). Also, among PET-negative patients during therapy, some patients relapse (Safar et al., 2012). Nonetheless, so far no studies support to change of treatment based on FDG-PET-scan during treatment, and thus outside clinical trials, it is not recommended to do FDG-PET-scans during therapy. However, patients with positive FDG-PET after immunochemotherapy could benefit of additional therapy, which needs to be studied in clinical trials. If possible, positivity should be confirmed with a biopsy.

5.5.8.2 Biological prognostic factors

Many of the proteins presented in the section about the biology of DLBCL (5.4.4 Genetics and immunophenotype) have been recognized as biological prognostic factors. Patients with ABC-DLBCL have shorter survival than patients with GCB DLBC, as described above (5.5.4 Molecular subtype) and even though the addition of R to chemotherapy has improved the survival for both GCB and ABC-DLBCL patients, the latter patients still have shorter survival (Pasqualucci 2013, Fu et al., 2008).

Hans algorithm (described in 5.5.5 Immunohistochemical algorithms) was reported to divide DLBCL to subtypes with prognostic difference similar to the one recorded with GEP-based division; GCB subtype has better prognosis than non-GCB subtype (Hans et al., 2004). However, the prognostic value of COO determined with immunohistochemistry is controversial. Some have reported a similar difference in survival according to COO determined with immunohistochemistry (Seki et al., 2009, Muris et al., 2006, Berglund et al., 2005, Sjo et al., 2007), while others found no difference (Amen et al., 2007, Dupuis et al., 2007, Moskowitz et al., 2005, De Paepe et al., 2005, Colomo et al., 2003). It was hypothesized that immunochemotherapy led to similar survival for both groups (Nyman et al., 2007, Seki et al., 2009), but later the survival difference has been confirmed even in immunochemotherapy treated patients (Fu et al., 2008, Abdulla et al., 2019, Ichiki et al., 2017). Also reports of lack of prognostic value of the Hans algorithm in patients treated with R-CHOP have been reported (Castillo et al., 2012, Ott et al., 2010).

Also other algorithms have been introduced, like Muris algorithm, which tried to differentiate patients according to survival (Muris et al., 2006, Sjo et al., 2007), Tally (Meyer et al., 2011), Nyman (Nyman et al., 2009b) and Choi (Choi et al., 2009). None of these have replaced Hans algorithm, however. Nor do the algorithms have an impact on the planning of the treatment (see 5.5.12 Treatment). The development of more precise sub-classification for DLBCL has therefore been important.

Expression of p53 has been recognized as predictor of outcome in DLBCL (Young et al., 2007, Hu et al., 2013). In addition, rearrangement of *MYC* has been reported to associate with poor prognosis in immunochemotherapy treated DLBCL patients (Barrans et al., 2010).

BCL6 has been reported as prognostic factor in immunochemotherapy treated DLBCL patients (Seki et al., 2009), whereas BCL2 has been recognized as prognostic factor in non-GC DLBCL patients treated with immunochemotherapy (Nyman et al., 2009a). As explained more comprehensively earlier, DPE of MYC and BCL2 or BCL6 is an adverse prognostic factor. (Sarkozy et al., 2015, Johnson et al., 2012)

In addition, numerous host related factors have been recognized as prognostic factors. Patients with low absolute lymphocyte count (ALC) and high absolute monocyte count (AMC) in whole blood have been reported to have shorter survival time (Bari et al., 2010, Wight et al., 2018, Porrata et al., 2012). On the other hand, patients with high immune cell count in tumour microenvironment have been reported to have longer survival time (Riihijarvi et al., 2015, Pollari et al., 2018, Leivonen et al., 2018).

5.5.9 Extranodal lymphomas and CNS spread

Lymphomas can occur also extranodally in any tissue. About 40% of DLBCL cases are initially confined to extranodal sites, gastrointestinal tract being the most common extranodal location (Swerdlow et al., 2017). The incidence for extranodal DLBCL is approximately 4.41 per 100 000 (2013-2017 data, web page of Finnish Cancer Registry, www.syoparekisteri.fi).

Numerous clinical characteristics have previously been recognized as risk factors of CNS spread, such as high IPI, high LDH, involvement of more than one extranodal site or age over 60 (Kridel, Dietrich 2011, Fletcher, Kahl 2014). In addition, extranodal DLBCL has been considered to be more aggressive and specifically to spread more often to CNS than nodal-DLBCL. Particularly DLBCLs in testis, adrenal gland, bone, breast, paranasal sinuses, parameningeal/epidural space, kidney and liver have been described to be prone to spread to CNS (Ghose et al., 2014). Median survival for patients with DLBCL spreading to CNS after treatment is less than 6 months (Ghose et al., 2014).

As described above (5.4.5 Prognostic factors), Schmitz et al. introduced CNS-IPI, which recognizes patient with high, i.e. 10.2% risk for CNS recurrence (Schmitz et al., 2016). Schmitz et al. had over 2100 patients in their model and over 1500 patients in their validation cohort, and thus our current understanding of risk of CNS spread of different extranodal locations is largely based on their report. In addition to IPI, their model identified kidneys and/or adrenal glands as risk factors for CNS spread. However, as mentioned earlier, the significance of skin as a high-risk location for CNS spread could not be evaluated, and on the other hand, in their validation set PT-DLBCL was recognized as a high risk extranodal location for CNS spread (Schmitz et al., 2016). Klankova et al. recently introduced a scoring system combining CNS-IPI score and COO, and showed patients with both high CNS-IPI and ABC/unclassifiable COO to have higher risk for CNS relapse (Klanova et al., 2019). In addition, HGBLs have both high risk of CNS recurrence and poor survival time (Schmitz et al., 2016, Kridel, Dietrich 2011).

The rituximab levels in cerebrospinal fluid are low (Rubenstein et al., 2003), but still according to some studies addition of R to chemotherapy has led to decrease in CNS recurrence rate. (Ghose et al., 2014, Murawski et al., 2014).

Earlier studies have not managed to show a benefit in the use of *it* CNS-directed treatment (Schmitz et al., 2016, Boehme et al., 2009, Schmitz et al., 2012, Kumar et al., 2012, Arkenau et al., 2007, Cheah et al., 2014). However, an intensified, CNS-directed therapy has been shown beneficial (Holte et al., 2013, Abramson et al,. 2010).

In previous clinical guidelines the patients with high-intermediate risk or high risk IPI, specifically patients with more than one extranodal site, elevated LDH or testicular, renal or adrenal involvement were recommended to have CNS prophylaxis (Tilly et al., 2015). In our 2019 updated national guidelines (https://www.onkologiayhdistys.fi), patients with high IPI, HGBL, PT-DLBCL, or with kidney and/or adrenal affision are recommended to gain CNS-directed treatment.

5.5.10 Sinonasal lymphomas

Sinonasal tract (SNT) DLBCL with yearly incidence of 0.06-0.17/100 000 is the most common SNT lymphoma in western population (Kanumuri et al., 2014, Dubal et al., 2015).

The classical symptoms that cause patient to contact their physician are swelling of lymph nodes or B-symptoms that are more common in advanced disease: night sweating, fewer and loss of weight (Shohat et al., 2004, Quraishi et al., 2000, Peng et al., 2014). In the case of SNT lymphoma, patients most often have nasal symptoms, yet bloody discharge is present in under 20% of the cases prior to diagnosis (Shohat et al., 2004, Quraishi et al., 2000).

In SNT lymphomas there is a long delay from first symptoms to diagnosis, which is explained by the unspecific nature of the symptoms and difficulty in getting representative tumour sample (Quraishi et al., 2000, Yen et al., 2012, Sands et al., 2008, Fajardo-dolci et al., 1999).

Biology of sinonasal tract DLBCL has not yet been studied thoroughly. In a Korean study in nasal and paranasal cavities GCB has been reported to account 12.5% of the DLBCL cases, whereas 58.7% have been reported as non-GCB (Lee et al., 2015). In a small Japanese study 82% of the SNT DLBCL cases were non-GCB, in addition, non-GCB was associated with inferior survival. (Carreras et al., 2017)

In SNT DLBCL varying involvement of head and neck locations makes the comparison of earlier reports difficult. However, the prognosis of extranodal craniofacial DLBCL treated with modern R based treatment has been considered to be similar with DLBCL in general (Murawski et al., 2014). In addition, risk of CNS spread has not been higher in paranasal or craniofacial DLBCL compared to DLBCL in general, whereas before the addition of R to chemotherapy, SNT and craniofacial DLBCL were associated with high risk of CNS spread. (Murawski et al., 2014, El-Galaly et al., 2017, Hausdorff et al., 1997, Laskin et al., 2005, Mian et al., 2013, Oprea et al., 2005, Kim et al., 2016)

5.5.11 Testicular lymphomas

PT-DLBCL comprises 1-2% of NHL, with an incidence of 0.09-0.26/100 000 (Gundrum et al., 2009, Moller et al., 1994, Vitolo et al., 2008, Zucca et al., 2003). Even though only 9% of all malignant testicular tumours are lymphomas, among patients over 50 years of age, they are the most common testicular malignancy (Moller et al., 1994, Vitolo et al., 2008, Zucca et al., 2003, Zucca et al., 1997).

Testicular expansion, is the most common symptom for primary testicular DLBCL patients to contact their physician (Moller et al., 1994, Ahmad et al., 2012). Often the symptom leads to ultrasound, which is followed by orchiectomy to gain histologic diagnosis. Example of a PT-DLBCL in ultrasound in Figure 5.9.

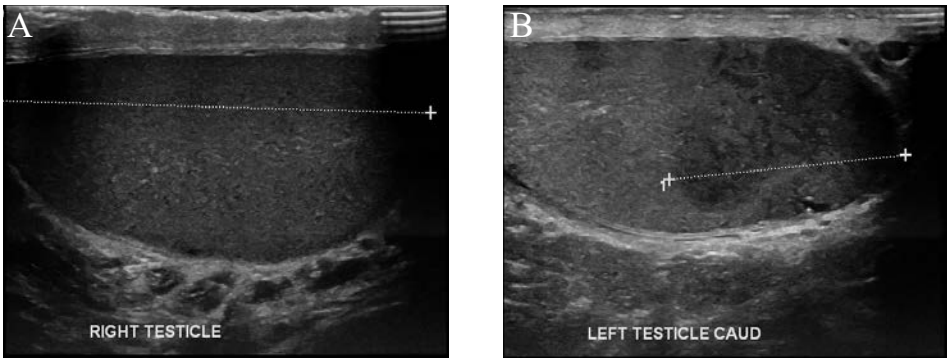

Figure 5.9 Ultrasound; A, normal testis; B, testis with confirmed DLBCL infiltration (markings)

PT-DLBCL has been reported to display non-GCB or ABC in over 75% of the cases (Twa et al., 2018, Deng et al,. 2016, Menter et al., 2014). Approximately 10% of PT-DLBCL cases have been reported to overexpress p53 (Menter et al., 2014). Rearrangements of *BCL6* are common and mutations in NF-κB-pathway genes (like *MYD88*, *CD79B* and *BCL10*) leading to the activation of NF-κB-pathway are common in PT-DLBCL (Twa et al., 2018, Menter et al., 2014). Also rearrangements of programmed death ligand 1 *(PDL-1)* and *PDL-2* genes occur (Twa et al., 2018). On the other hand, rearrangements in *BCL2* or *MYC* are rare (Menter et al., 2014).

Interestingly, also the tumour microenvironment of the lymphoma cell has prognostic impact in PT-DLBCL, as our group has earlier reported: the expression of programmed death 1 (PD-1) ligand PDL-1 in tumour infiltrating macrophages as well as PD-1 in tumour infiltrating lymphocytes associates with favorable survival in PT-DLBCL (Pollari et al., 2018).

The addition of R to chemotherapy has led to modest improvement in survival in PT-DLBCL (Deng et al., 2016, Cheah et al., 2014, Gundrum et al., 2009, Vitolo et al., 2008, Ahmad et al., 2012, Kridel et al., 2017, Vitolo et al., 2011, Aviles et al., 2009). PT-DLBCL has still been reported to have high risk of spreading to contralateral testis and CNS, and the prognosis of PT-DLBCL is still worse compared to prognosis of DLBCL in general (Deng et al., 2016, Schmitz et al., 2016, Vitolo et al., 2008, Ahmad et al., 2012, Vitolo et al., 2011, Siegal, Goldschmidt 2012, Cheah et al., 2014). As lymphoma cells may be protected in the contralateral testis during chemotherapy, the contralateral is recommended to be treated with irradiation or orchiectomy (Tokiya et al., 2017, Ho et al., 2017).

5.5.12 Treatment

Without treatment, DLBCL leads to death. The treatment of DLBCL has evolved over time, as described above (5.1 Background). Fischer et al. showed in their phase III study in 1994 no other treatment managed to outperform CHOP, yet fatal toxicity occurred less frequently among patients treated with CHOP compared to other available chemotherapies (Fisher et al., 1994). CHOP is still today the backbone of DLBCL treatment.

In addition, modern treatment with CD20 monoclonal antibody rituximab has led to marked improvements in the treatment results (Feugier et al., 2004, Coiffier et al., 2002, Coiffier et al., 2010, Habermann et al., 2006, Cunningham et al., 2013, Delarue et al., 2013, Pfreundschuh et al., 2008, Pfreundschuh et al., 2006). First, R-CHOP therapy was shown to lead to longer survival compared to CHOP in a randomized trial in elderly (60-80y) patients, with no significant difference in toxicity, later validated in 10y follow-up (Coiffier et al., 2002, Coiffier et al., 2010). Subsequently, the addition of maintenance R to conventional R-CHOP was not shown to lead to longer survival compared to R-CHOP treatment alone (Habermann et al., 2006). The benefit of R-CHOP over CHOP alone in young patients with low risk was also shown (Pfreundschuh et al., 2006). The amount of R cycles was also studied, and six cycles was not shown to be inferior to eight cycles, and actually patients receiving six cycles had longer survival, probably because of fewer toxicity related problems (Pfreundschuh et al., 2008). Also, there is no difference in survival when administering R every two weeks instead of every three weeks (Cunningham et al., 2013, Delarue et al., 2013).

About 74% of the patients receiving immunochemotherapy have been reported to remain event free in 6-year follow-up, compared to 56% among 18-60 year old patients receiving chemotherapy (Pfreundschuh et al., 2011), whereas among 60-80 year old patients the 10-year PFS for patients receiving immunochemotherapy has been reported as 37% compared to 20% among patients receiving chemotherapy (Coiffier et al.,. 2010). Indeed, introduction of monoclonal CD20 antibody rituximab has improved survival of DLBCL so much that the time after the introduction of rituximab is even called R-era.

The experience from our own institution showed patients treated with R-CHOP had OS of 72% at 3.5 years, as opposed to 49% among patients receiving CHOP, with the greatest difference in survival among high risk patients; patients with IPI 3-5, treated with R-CHOP OS 65% at 3.5years; patients with IPI 3-5, treated with CHOP OS 27% at 3.5 years (Leppä et al., 2009).

Interestingly, in a phase III study, patients treated with dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (R-ACVBP) had PFS of 87% and OS of 92% at 3y, as opposed to PFS of 73% and OS of 84% for patients treated with R-CHOP (Recher et al., 2011).

A recent phase III trial on over 50 000 patients, majority (74%) with Stage III or IV disease, found patients treated with dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) did not have longer survival compared to R-CHOP treated patients, but patients in DA-EPOCH-R group had more adverse events. However, in a post hoc analyses, they found patients with high IPI

(IPI 4-5) to have higher PFS if treated with DA-EPOCH-R, but they did not find significant difference in OS. (Bartlett et al., 2019)

Even though there are numerous trials trying to find more effective and more personalized treatments for patients according to the molecular subtype of the tumour, in normal clinical practice the treatment is still chosen according to clinical risk factors – like age or IPI.

Current standard primary therapy for DLBCL is R-CHOP, consisting of acylating agent cyclophosphamide that damages DNA and prevents DNA synthesis and RNA transcription from DNA, hydroxydaunorubicine that also causes DNA damage, vincristine that binds to tubulin and thus interferes mitosis, and prednisone. Combination of etoposide to R-CHOP (i.e. R-CHOEP-treatment) is used for young high-risk patients. Etoposide causes errors in DNA synthesis and thereby apoptosis in fast dividing cells.

Chimeric CD20 antibody rituximab binds to CD20 causing its relocation into lipid-rafts, leading to initiation of complement (Cragg et al., 2003). Complement and antigen dependent cytotoxicity are important in the mechanism of action of rituximab (Ku et al., 2017, Boross, Leusen 2012).

For relapse, a histologic confirmation of the disease is highly recommended. According to national guidelines (https://www.onkologiayhdistys.fi), platinum based immunochemotherapy is used for first relapse, possibly added with autologous transplantation (see Table 5.5). New treatments are forthcoming, and for second relapse also CD19 targeted chimeric antigen receptor (CAR) T-cell therapies are applied (see below 5.7.1 Novel therapies and Table 5.5).

Methotrexate inhibits DNA synthesis through inhibiting dihydrofolate reductase whereas cytarabine inhibits DNA polymerase. Earlier immunochemotherapy was combined with CNS-directed *it* methotrexate (MTX), but nowadays intravenously (*iv*) administered high-dose (HD)-MTX is recommended for patients considered to have high risk for CNS recurrence, or if MTX is not possible, HD-cytarabine (see in more detail 5.5 Extranodal lymphomas and CNS spread).

Table 5.5 (modified from national guidelines https://www.onkologiayhdistys.fi and Tilly et al., 2015) IPI, international prognostic index; aaIPI, age-adjusted IPI; DH, double-hit; R, rituximab; CHOP, cyclophoshpamidie, hydroxydaunorubicine, vincristine, prednisone; IF-RT, involved field radiotherapy; HDCT, high-dose chemotherapy; ASCT, autologous stem-cell transplantation; DHAP, cisplatin, cytarabine, dexamethasone; ICE, ifosfamide, carboplatin, etoposide; GDP, cisplatin, gemcitabine, dexamethasone; CHOEP, CHOP with etoposide; R-C(X)OP, R-CHOP with substitution of hydroxydaunorubicine; CAR-T chimeric antigen receptor T-cell

Recommendation of treatment in DLBCL		
Patients ≤ 60y	*IPI low or low-intermediate risk (aaIPI 0-1)*	IPI intermediate-high or high risk (aaIPI 2-3), DH lymphomas
	R-CHOP21x6 (+IF-RT for bulky tumour)	R-CHOP21x6-8 R-CHOP14x6 with 8R or R-CHOEP 14x6
CNS prophylaxis consideration for patients at risk for CNS progression		
Elderly >60y		
Fit 60-80y	>80y without cardiac dysfunction	Unfit or >60y with cardiac dysfunction
R-CHOP21x6-8 or R-CHOP14x6 with 8R	R-miniCHOP21x6	Doxorubicin substitution with gemcitabine, etoposidine or liposomal doxorubicine or others: R-C(X)OP21x6 or palliative care
Consider CNS prophylaxis for patients at risk		
First relapse/progress	Eligible for transplant	Not eligible for transplant
	Platinum based regimens (like R-DHAP, R-ICE, R-GDP) or R-HDCT with ASCT	Platinum based regimens or Clinical trials with novel drugs
>2 relapse/progress	Allogenic transplantation CAR-T therapy for WHO 0-1 patients Clinical trials with novel drugs	Clinical trials with novel drugs or Palliative care

5.5.13 Novel therapies

The patients with ABC DLBCL still have shorter survival time and previously referred locations are considered high risk for CNS spread (see 5.4.5 Prognostic factors and 5.5.9 Extranodal lymphomas and CNS spread). Cardiotoxicity of anthracycline on the other hand produces challenges. Novel therapies are studied to answer these clinical challenges and to provide more treatment options.

Pixanthrone has been shown to be effective in relapsed or refractory NHL patients, and to have low cardiotoxicity compared to anthracycline (Barrenetxea Lekue et al., 2019). Even though relapsed patients may remain sensitive for anthracycline, the cumulative toxicity restricts their use and therefore, pixanthrone is a needed option for relapsed NHL patients. In a phase III study pixantrone as a single-agent salvage therapy was shown to be effective and tolerable in patients with relapsed or refractory aggressive NHL (Pettengell et al., 2012). Pixanthrone could also be used as part of first line treatment for patients for whom the cardiotoxicity of anthracycline could cause problems, as R-CPOP -treatment (Barrenetxea Lekue et al., 2019).

Next generation CD20 antibodies have been introduced, like ofatumumab and obinutuzumab, but these have not been shown to have better survival compared with R (van Imhoff et al., 2017, Vitolo et al., 2017). In addition, monoclonal antibodies for other B-cell antigens, like CD19 or CD22 have been introduced. Many of them have different kind of mechanism of action than rituximab, like engaging T-cells with targeted B-cells. (Ku et al., 2017)

Bruton Tyrosine Kinase (BTK) inhibitor ibrutinib has been shown to inhibit chronically active B-cell receptor (BCR) signalling in ABC DLBCL and could be used in many ABC DLBCL patients. Nonetheless, approximately 10% of ABC DLBCL cases have mutations in this pathway making them resistant for BTK inhibitors. In addition, other inhibitors targeting BCR signalling pathway are being studied in clinical trials. In the future, we need to classify and treat DLBCL cases according to their mutational profile and signalling pathway they use (Basso, Dalla-Favera 2015, Pasqualucci, Zhang 2016, Young, Staudt 2013, Pasqualucci, Dalla-Favera 2018). In a recent phase III trial the addition of ibrutinib to R-CHOP improved survival in patients younger than 60 years with non-GCB DLBCL, whereas among patients 60 years of age or older, it increased serious adverse events and the proportion of patients receiving at least six cycles of R-CHOP was decreased (Younes et al., 2019).

Lenalidomide is an immunomodulatory agent. When compared to other treatment in phase II/III study, lenalidomide has been reported to be beneficial on relapsed DLBCL patients, in the subgroup of non-GCB patients the benefit was greater than in GCB patients (Czuczman et al., 2017). In REMARCH study Thieblemont et al. showed lenalidomide maintenance therapy after R-CHOP prolonged PFS. The result was more clear among low risk (IPI 1-2) patients (Thieblemont et al., 2019). Also, the lenalidomide maintenance therapy among patients that had received six cycles of R-CHOP had led to a trend towards longer PFS

compared to patients that had received eight cycles or R-CHOP prior to lenalidomide maintenance therapy (Thieblemont et al., 2019).

According to a recent meta-analysis, bortezomib, a proteasome inhibitor, did not prolong survival of ABC DLBCL patients, even though it has been reported to show activity especially in ABC DLBCL (Lin et al., 2018). In addition, in a small phase II trial on relapsed/refractory DLBCL (39 patients with DLBCL), it showed very limited activity, with overall response rate 7.7% (Yazbeck et al., 2018). In a phase III study with 1128 patients the addition of bortezomib showed no improvement in PFS (Davies et al., 2019).

Chapuy et al. reported that there is increased expression of PD-1 ligands in PT-DLBCL (Chapuy et al., 2016). In addition, PD-1 blockade has proven to be effective new treatment. Cancer cells express PD-1 ligands PD-L1 and PD-L2 and thus through activation of PD-1 on T cells inhibit T-cell activity. PD-1 blockade with nivolumab has shown promising results in primary testicular and CNS lymphoma, but needs to be studied in prospective clinical trials. (Nayak et al., 2017)

Also bispecific T-cell enganging antibody constructs have been shown to have efficacy in relapsed or refractory DLBCL patients (Goebeler et al., 2016, Viardot et al., 2016). Blinatumomab is a construct that connects CD19 positive B-cells with CD3 positive T-cells, thus inducing the activation of T-cell-mediated tumour cell lysis (Baeuerle, Reinhardt 2009, Molhoj et al., 2007, Hoffmann et al., 2005). In a phase II study on relapsed or refractory DLBCL patients blinatumomab monotherapy led to responses in over 40% of the patients, with median PFS of 3.7 months for patients evaluable for efficacy evaluation (Viardot et al., 2016). The longest recorded PFS so far was over 20 months and still without an event (Viardot et al., 2016).

Relapsed of refractory DLBCL has had a poor prognosis. In a recent retrospective study, 26% of the patients with refractory DLBCL were reported to have response to standard therapy. The median survival was reported to be six months (Crump et al., 2017). However, chimeric antigen receptor (CAR) T-cell treatments targeting CD19 or CD20 receptor of B-cells are changing treatment strategies for relapsed B-cell malignancies, including DLBCL (Maude et al., 2014, Maus et al., 2014, Kochenderfer et al., 2015). CD8+ T-cells are harvested from patients own blood and genetically engineered to express an anti CD19 CAR and then infused back to patient (Maus et al., 2014). In a phase I-II trial 82% of patients with refractory DLBCL and treated with CAR-T were reported to have an objective response (Neelapu et al., 2017). In a long term follow-up report, the same group reported OS of the patients to be greater than two years, with 2-year OS of 51% (Locke et al., 2019). In a phase II trial, an overall response rate of even 52% was reported (Schuster et al., 2019). CAR-T treatment offers possibility to cure eligible patients with refractory B-cell malignancies, but the adverse side effects, as cytokine release syndrome, set a challenge. However, CAR-T treatment is a very potential new therapy that offers the possibility for cure. According to national treatment guidelines in Finland (https://www.onkologiayhdistys.fi), CAR-T therapy is recommended for patients with relapse after second line treatment for WHO 0-1 patients.

5.5.14 Response evaluation and follow up

Response evaluation after treatment is defined with FDG-PET-CT (Tables 5.6 and 5.7) or CT (Table 5.7). In CT lymph nodes under 1.5cm in diameter are considered normalized. In FDG-PET-CT 5-point scale Deauville criteria is used for response evaluation; scores 1 and 2 are considered as complete metabolic response (Cheson et al., 2014, Valls et al., 2016). Also, patients with score 3 at the end of the treatment have good prognosis, but in an interim scan in clinical trials it is considered as an inadequate response, in order to avoid undertreatment (Valls et al., 2016, Pregno et al., 2012). Scores 4 and 5 refer to active disease and treatment failure, even if activity had declined from pretreatment scan. Scores 4 and 5 with increasing activity refer to progressive disease. (Cheson et al., 2014, Valls et al., 2016)

Table 5.6 Deauville criteria (modified from Valls et al., 2016)

Score	Deauville criteria
1	No increased FDG uptake
2	FDG uptake ≤ mediastinum
3	mediastinum < FDG uptake ≤ liver
4	FDG uptake moderately higher than in liver
5	FDG uptake clearly higher than liver or new lesions
X	New areas of FDG uptake unlikely to be related to lymphoma

As earlier described, it is important to confirm relapse histologically, as scar tissue or inflammation might resemble relapse, or patient might have another malignancy.

In DLBCL, the likelihood of recurrence decreases over time, the follow-up visits take place more often in the beginning, with longer intervals after two years (Cheson et al., 2014, Cheson et al., 2007). In our national guidelines, a follow-up visit every 3-6 months is recommended during the first two years, and after that every 12 months, with a total follow-up time of 5 years (https://www.onkologiayhdistys.fi).

Early detection of the (residual) tumour is under active research. Circulating tumour DNA (cDNA) offers a new interesting diagnostic approach. It is released to circulation after apoptosis of tumour cells and reflects the tumour burden and molecular heterogeneity of the disease and thus could be used in early detection of the disease, in evaluation of treatment response and detecting residual tumour (Diaz, Bardelli 2014, Roschewski et al., 2016, Scherer et al., 2016, Rossi et al., 2017). However, cDNA is not yet used in clinical decision-making.

Table 5.7 DLBCL response criteria (modified from Cheson et al., 2014, Valls et al., 2016)

Response category	CT response criteria	PET response criteria
Complete Response (CR)	Longest diameter of target nodes regressed to ≤1.5cm	Nodes and extralymphatic sites: score 1-3
	No extralymphatic sites of disease	No new lesions
	No new lesions	Organ enlargement normalized
	Organ enlargement normalized	No FDG uptake in bone marrow
	Bone marrow morphology normal	
Partial Response (PR)	≥50% decrease in sum of perpendicular diameters of up to 6 target measurable nodes and extranodal sites	Nodes and extralymphatic sites: score 4-5 with reduced uptake compared to baseline
	No new lesions	No new lesions
	Length of spleen exceeding normal regressed by 50%	Residual uptake in normal bone marrow but reduced compared to baseline
Stable Disease (SD)	<50% decrease in sum of perpendicular diameters of up to 6 dominant measurable nodes and extranodal sites	Nodes and extralymphatic sites: score 4-5 with no significant change in uptake intensity compared to baseline
	No increase in organ enlargement or in non-measurable lesions (referring to progression)	No new lesions
	No new lesions	No change in bone marrow from baseline
Progressive Disease (PD)	An abnormal node/lesion >1,5cm in longest diameter and increase in diameter	Nodes and extralymphatic sites: score 4-5 with an increase in intensity of uptake from baseline
	New lesions or progression in pre-existing non-measured lesions	New extranodal foci
	New or recurrent splenomegaly or bone marrow involvement	New or recurrent foci in bone marrow

6 Aims of the study

Extranodal DLBCL is considered to spread more often to CNS than nodal DLBCL. The hypothesis was that DLBCL cases occurring at various extranodal locations could have common characteristics and could share prognostic factors. Especially it was hypothesized that DLBCL at various extranodal locations could share prognostic factors for CNS spread. Two extranodal DLBCLs, sinonasal and testicular, were selected to study the hypothesis.

First, the aim was to study the epidemiology of SNT lymphomas. This study aimed to categorize immunologic profile of SNT DLBCL, which was not well known. The present study intended to study the differences in survival among patients with different immunologic profiles. In addition, one aim of this study was to study what kind of therapies SNT DLBCL patients have been given, and the outcome of patients in response to different therapies.

For men with PT-DLBCL, radiotherapy is often given to the non-affected contralateral testis, or it is removed surgically. The impact of this treatment on prognosis and on CNS recurrence was aimed to test here. The impact of R therapy and CNS-directed therapy (*iv* or *it*) on survival and on CNS recurrence in PT-DLBCL was also planned to explore.

One aim of this study was also to find out, if blood cell counts could be used to identify patients with worse prognosis. Therefore, ALC and AMC in whole blood were analysed to study their prognostic significance in PT-DLBCL.

The aims of the study were to

1) describe the epidemiology and anatomic division of SNT lymphomas
2) compare survival rates of SNT DLBCL patients in response to different therapies and describe the immunologic profile of SNT DLBCL
3) compare survival rates of PT-DLBCL patients in response to different therapies including treatment of contralateral testis
4) define prognostic impact of ALC and AMC in patients with PT-DLBCL

7 Patients, materials and methods

7.1 Patients

Nasal cavities, paranasal sinuses and nasopharynx were considered to constitute SNT. The Department of Pathology databases at Helsinki University Hospital (Helsinki Finland) and the Tampere University Hospital (Tampere, Finland) were searched for the patients with lymphoid malignancies in the SNT area. Also, the nationwide Finnish Cancer Registry (communication with Malila N., 2015) was searched for the patients with SNT lymphoid malignancies. The hospital records for these patients were retrospectively reviewed and follow-up data collected. Primary CNS lymphomas were excluded. (I and II)

For PT-DLBCL the pathology databases of Helsinki, Tampere and Turku University Hospitals and the Danish lymphoma registry were searched for PT-DLBCL. The hospitals records for the Finnish patients were retrospectively reviewed and the data of Danish patients was collected from the lymphoma registry (Arboe et al., 2016). For instance, patient gender, age at diagnosis, the exact treatment, the date of the onset of the treatment and the date of the onset of possible CNS directed therapy, blood cell values, IPI-factors and survival data, including date of possible CNS spread, were collected. Primary CNS lymphomas were excluded and only primary PT-DLBCL lymphomas were included in the study. (III and IV)

Practically all patients diagnosed with lymphoma in Southern Finland in the referral areas are treated at these hospitals and the Danish lymphoma registry has nationwide coverage in Denmark.

The number of patients in each publication is shown in Table 7.1. The data for Publications I and II was collected 2014-2015. The Finnish patients for Publication III and IV were collected 2014-2015 and the Danish patients 2017.

Statistics Finland provided population data for each year for incidence calculations. (I and data published in this manuscript)

Table 7.1 Number of patients, timeframe of the year of diagnosis, number of patients in biological analysis and median follow-up time according to publication.

	Publication I	Publication II	Publication III	Publication IV
Number of patients (n)	142	63	235	178
Timeframe of diagnosis	1975-2013	1977-2015	1987-2013	1987-2013
Number of patients in biological analysis	-	47	74	-
Median follow-up time (months)	-	47	81	55

7.2 Tumour sample analysis

Pathology reports were reviewed for the Finnish SNT and PT-DLBCL patients, diagnostic tissue blocks were collected and tissue microarray (TMA) blocks constructed. For immunohistochemistry 5µm sections were used. Lymphoma diagnosis was reviewed according to the current WHO classification together with a hematopathologist. (Swerdlow et al., 2017). (I-IV)

Standard diagnostic immunohistochemistry using antibodies for CD79, CD10, BCL2, BCL6, melanoma-associated antigen 1 (MUM1) and MYC was used for the TMA. Examples of immunohistochemistry are shown in Figure 7.1. Cell of origin (COO) was defined according to the Hans algorithm (Figure 5.4) (Hans et al., 2004). (I-IV)

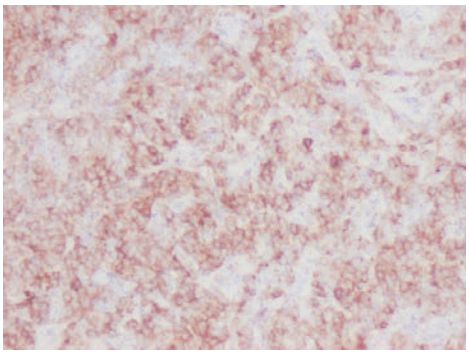

Figure 7.1A

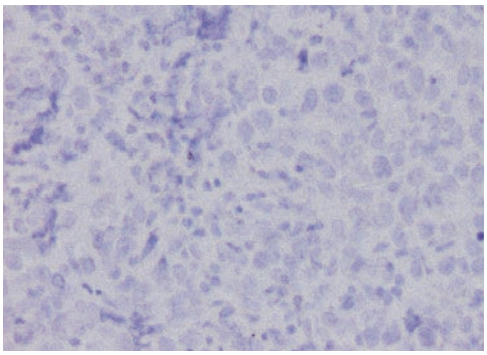

Figure 7.1B

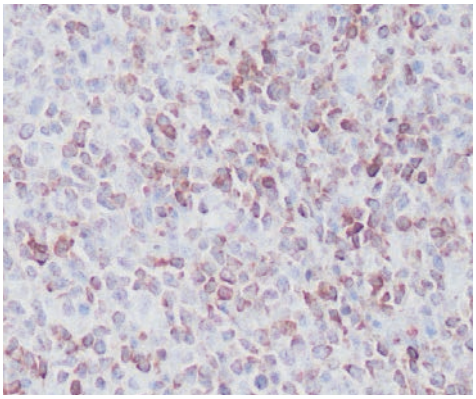

Figure 7.1C

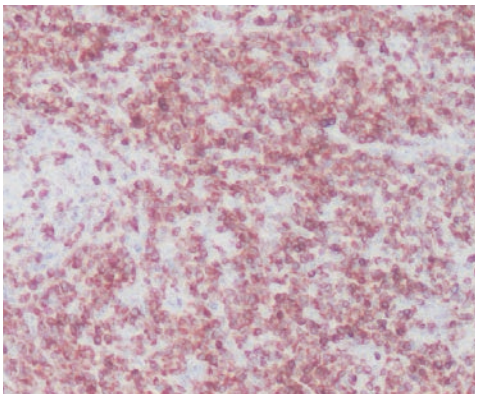

Figure 7.1D

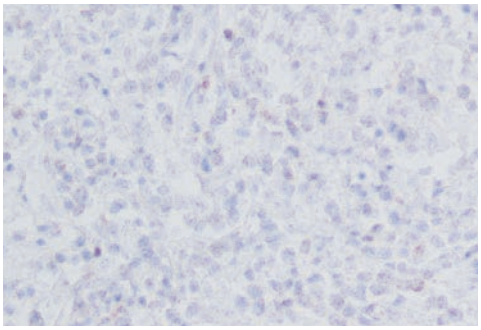

Figure 7.1E

Figure 7.1; A, SNT DLBCL sample with CD10 positive lymphoma cells (in brown); B, SNT DLBCL sample with CD10 negative lymphoma cells (in blue); C, PT-DLBCL with BCL2 positive (brown) and BCL6 negative lymphoma cells; D, PT-DLBCL with BCL2 positive (brown) and BCL6 positive (red) lymphoma cells; E PT-DLBCL with BCL2 and BCL6 negative (blue) lymphoma cells

7.3 Absolute lymphocyte and absolute monocyte counts

The lower limit of normal ALC in whole peripheral blood at our institution (laboratory of Helsinki and Uusimaa hospital district) is ALC=1.3 $x10^9$/l. Patients were divided into two subgroups according to ALC using as cut-off value this lower limit of ALC gaining two subgroups, lymphopenic and non-lymphopenic patients.

Patients were divided into two groups for survival analyses also by lymphocyte to monocyte ratio (LMR). The earlier reported cut-off value of 3:1 for LMR was used as cut-off value in the analysis (Wight et al., 2018, Lin et al., 2015).

(IV)

7.4 Statistics

The X^2 test was used to evaluate the differences between patient groups in baseline characteristics and used treatments. The prognostic value of the baseline factors and used treatments were evaluated with Cox univariate regression analyses. Kaplan-Meier method was used to estimate survival rates and the differences in the results were compared with log-rank test. All p-values were two-tailed and p-values ≤ 0.05 were considered significant.

Progression-free survival (PFS) was calculated from date of diagnosis till the date of relapse or death from any cause and overall survival (OS) was calculated from date of diagnosis till death from any cause. Disease-specific survival (DSS) was calculated from date of diagnosis till date of death caused by treatment or lymphoma.

SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) was used for all statistical analyses.

(I-IV)

7.5 Ethical aspects

The study is retrospective aiming to increase the knowledge of sinonasal and testicular DLBCL, which might lead to better treatment and longer survival in the future. As many of the patients had already passed away at the time of the study and thus could not give their consent, the study and sampling were approved by the Institutional Review Boards, Ethics Committees and Finnish National Supervisory Authority for Welfare and Health. Data was collected from archives and therefore, no additional investigations or interventions were made to the patients involved in the present series. Lymphoma tissue was collected from archives for biological analyses and therefore did not cause any extra discomfort for the patients.

(I-IV)

8 Results

8.1 Symptoms, epidemiology and distribution of sinonasal lymphomas

An increasing trend of SNT lymphoid malignancies was discovered, as well as an increasing trend of SNT DLBCL in Finnish population. The incidence of SNT DLBCL has grown even by 70% from 1985-1994 to 2005-2013 (Publication I Figure 2).

Majority of the SNT patients had nasal symptoms prior to diagnosis, and nasal symptoms were the most common type of symptoms. In addition, often patients had many kinds of symptoms. Bloody discharge was reported in 31% of the cases. Pharyngeal and laryngeal symptoms were reported a bit more often, in 34% of the cases, whereas ear and eye/vision symptoms were less common (18% and 15%, respectively). The duration of symptoms was available for 124 patients. On average, the patients had had symptoms 4.8 months prior to diagnosis (range 0.5-24 months).

Majority of the SNT cases were primary SNT malignancies (84%). DLBCL was the most common malignancy in both primary disease (46% of the cases) and in SNT as secondary or relapse location (26%). Plasmocytomas were the second most common primary SNT disease (18%).

Nasopharynx was the most common as a single SNT location (39%), whereas nasal cavity was recorded as a single location in 19% of the cases and paranasal sinuses only in 11% of the cases. The disease had spread to both nasal cavity and nasopharynx in 6% of the cases, nasopharynx and paranasal sinuses in 6% of the cases and nasal cavity and paranasal sinuses in 11% of the cases. Disease in nasopharynx, nasal cavity and paranasal sinuses was reported in 7% of the cases, and the one patient with missing data had very likely a tumour reaching several SNT areas.

The majority of the patients had Stage I disease (52%). Stage II and III were less common (13% and 10%, respectively) and Stage IV disease was recorded in 22%. The Stage could not be determined for 3% of the patients.

8.2 Treatment outcome and immunohistologic profile of SNT DLBCL

Totally 63 SNT DLBCL patients diagnosed 1977-2015 were identified. CHOP or CHOP-like chemotherapy had been given to 46 patients. For 25 patients, R had been added to the CHOP or CHOP-like treatment (R-chemo), whereas 21 patients had received CHOP or CHOP-like chemotherapy without R (non-R). CNS-directed treatment (*iv* HD-MTX, *it* MTX or *iv/it* cytarabine or combination of these) had been given as part of the treatment for 24 (52%) patients. Radiotherapy had been part of the treatment for 18 patients (39%).

Sixty-five percent of the patients were male and 52% of the patients were 60 years of age or older. Seventy-four percent of the patients had Stage I-II disease, whereas LDH was elevated in 40% of the patients. Patients receiving CNS-directed therapy were younger than other patients (<60 years, 67% vs 27%, p=0.010). On the other hand, patients not receiving R as part of their treatment were more often treated with radiotherapy as part of their treatment compared to patients that did receive R as part of their treatment (62% for patients not treated with R vs 39% for patients treated with R, p=0.003). Other significant differences in baseline characteristics were not recorded.

Location of the tumour was not significantly associated with known risk factors, nonetheless patients with tumour in paranasal sinuses were more often treated with CNS-directed treatment as part of their chemotherapy than other patients (80% vs 35%, p=0.010). The tumour location was counted for each location the tumour reached.

Lymphoma tissue was available for 47 patients for immunohistochemistry analyses. Cell of origin was determined according to Hans algorithm (Hans et al., 2004). GCB tumours appeared in younger patients than non-GCB tumours (<60 years old; 63% vs. 28%; p=0.029). High LDH was recorded more often for BCL2 negative cases than for BCL2 positive (80% vs. 32%, p=0.040). BCL2 positive cases got less frequently CNS-directed chemotherapy compared with BCL2 negative cases (40% vs 83%, p=0.045). Cases positive for MYC and BCL2 were more frequent than the reported share in DLBCL in general (61% vs 17-29%) (Johnson et al., 2012, Green et al., 2012, Molina et al., 2014, Staiger et al., 2017). High LDH was recorded more often for cases that were DPE or triple protein expressors than for others (57% vs none, p=0.017).

In nasal cavity location 88% of the tumours were BCL2 positive and 81% BCL6 positive. CD10 positivity was recorded in 27% of tumours in nasal cavity and MYC positivity in 38%. Twenty-seven percent of the tumours in nasal cavity were GCB. Thirty-eight percent of the tumours in nasal cavity were DPE or triple protein expressors.

For tumours in paranasal sinuses 81% of the tumours were BCL2 positive and 86% BCL6 positive. CD10 positivity was recorded in 19% of the cases in paranasal sinuses and MYC positivity 33%. Forty-seven percent of the tumours in paranasal sinuses were GCB. In paranasal sinuses 33% of the tumours were DPE or triple protein expressors.

Eighty-eight percent of the tumours in nasopharynx were BCL2 positive and 83% BCL6 positive. CD10 positivity was recorded in 29% and MYC positivity in 77% of the tumours in nasopharynx. Seventy-seven percent of the tumours in nasopharynx were DPE or triple protein expressors.

Among all SNT tumours, 87% were BCL2 positive and 87% were BCL6 positive. Twenty-four percent were CD10 positive and 67% MYC positive. Thirty-two percent were GCB phenotype among all SNT tumours. Among all SNT tumours 63% were DPE or triple protein expressors.

Nineteen patients out of the 46 patients treated with curative intent relapsed and 14 died during the 60 months follow-up time (median follow-up time 47 months). Five-year PFS was 51% and OS 63% (Figure 8.1). During the follow-up time, one CNS progression occurred.

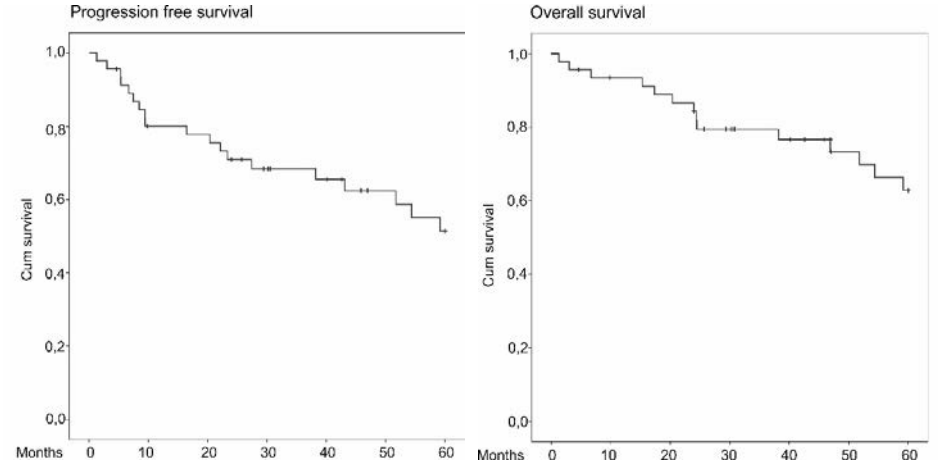

Figure 8.1 PFS and OS for SNT DLBCL patients treated with curative intent

The location of the lymphoma or known clinical risk factors did not correlate with the survival in cox-regression analyses.

R-chemo treated patients had reduced risk of progression and death compared with non-R treated patients (PFS RR 0.368, 95% CI 0.138-0.976, p=0.045; OS RR 0.245, 95% CI 0.068-0.883, p=0.032). Also longer survival time was recorded for R-chemo treated patients compared with non-R treated (5-y PFS 67% vs 38%, p=0.037; 5-y OS 81% vs 48%, p=0.020; Publication II, Figure 1).

In addition, CNS-directed chemotherapy treated patients had lower risk of progression and death compared with patients not receiving CNS-directed chemotherapy (PFS RR 0.404, 95% CI 0.159-1.029, p=0.057; OS RR 0.298, 95% CI 0.093-0.950, p=0.041). Also longer survival was recorded for patients treated with CNS-

directed chemotherapy compared with patients not treated with CNS-directed chemotherapy (5-y PFS, 67% vs 32%, p=0.050; 5-y OS 82% vs 43%, p=0.030; Publication II, Figure 2).

Patients treated with combination of R-chemo and CNS-directed chemotherapy had the longest survival (5-y PFS, 74%; 5-y OS 100%). Patients that were treated with R-chemo but did not receive CNS-directed chemotherapy *5*-y PFS was 61% and 5-y OS 60%. Patients in non-R group but treated with CNS-directed chemotherapy 5-y PFS was 55% and 5-y OS 64%. Patients in non-R group and not treated with CNS-directed chemotherapy had the shortest survival (5-y PFS 20% and 5-y OS 30%, PFS p=0.037 and OS p=0.015; Publication II, Figure 3).

As the oldest patients did not receive CNS-directed chemotherapy, we decided to study separately patients younger than 76 years of age and treated with (R-)CHOP or alike (immuno)chemotherapy. Median age in this subgroup was 58 years. Known risk factors were equally distributed between the treatment groups (R-chemo vs non-R-treated and CNS-directed vs patients not treated with CNS-directed). CNS-directed chemotherapy was given also evenly often for R-chemo and non-R-treated patients.

Among the patients younger than 76 years, R-chemo patients had lower risk of progression and death (PFS RR 0.250, 95% CI 0.09-0.888, p=0.033; OS RR 0.116, 95% CI 0.015-0.917, p=0.041). R-chemo patients had, also in this subgroup of younger patients, longer survival than non-R-treated (5-y PFS 74% vs 40%, p=0.021; 5-y OS 94% vs 50%, p=0.013). Likewise more aggressive treatment with CNS-directed chemotherapy led to reduced risk of progression and death (PFS RR 0.432, 95% CI 0.156-1.194, p=0.105; OS RR 0.297 95% CI 0.087-1.016, p=0.053) and was linked with longer survival time (5-y PFS, 67% vs 34%, p=0.096; 5-y OS 82% vs 42%, p=0.040)

Cell of origin (COO) and survival data were available for 41 patients, whereas BCL2 expression was available for 44 and BCL6 analyses for 42 patients. There was no difference in PFS or OS of patients according to COO immunophenotype or according to BCL2 or BCL6 expression.

ALC or AMC did not significantly correlate with survival in the group of patients with SNT DLBCL in this study.

8.3 Risk factors and treatment of PT-DLBCL

The incidence of PT-DLBCL according to the population of each year in the referral area of the Southern Finnish university hospitals was determined. The incidence has increased over the study period in Southern Finland (Figure 8.9).

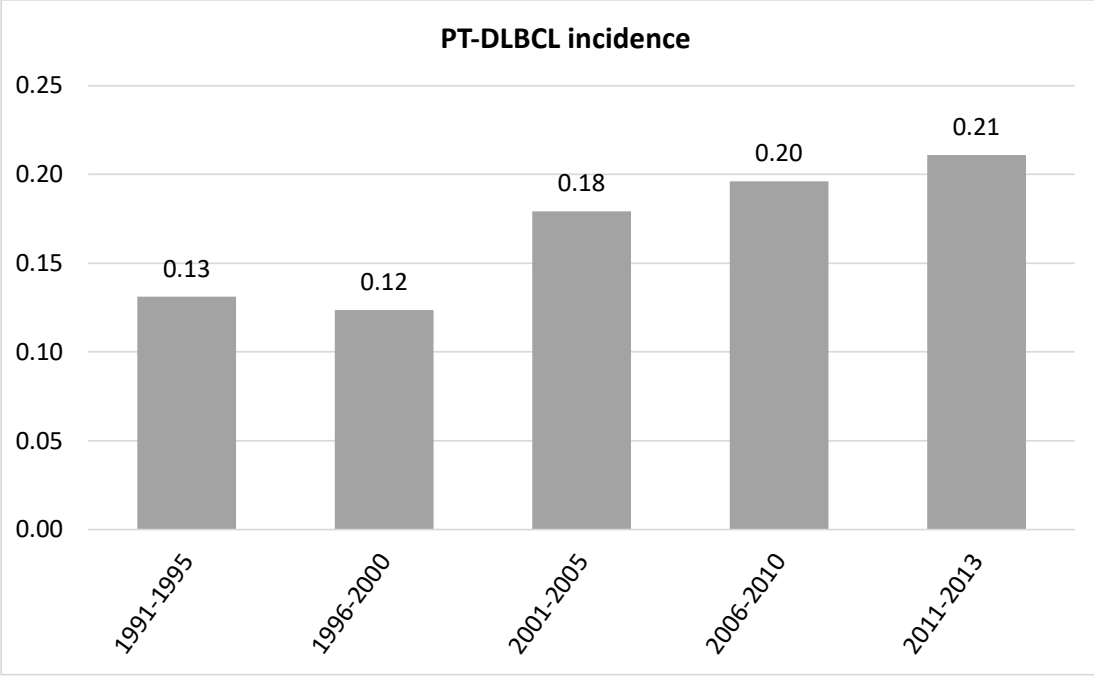

Figure 8.9 Incidence of PT-DLBCL per 100 000 citizens in Southern Finland

We identified 235 PT-DLBCL patients treated between 1987 and 2013. Ten per cent of the Finnish patients had involvement of both testes, but in the Danish lymphoma registry, involvement of both testes was not specified. Patients with CNS involvement at diagnosis were excluded from the study.

Complete survival data was available for 189 patients treated with CHOP-like treatment. One hundred-twenty of them (63%) were treated with R as part of the treatment and 69 (37%) without R. Seventy-six patients (40%) out of the total number of 189 patients received CNS-directed treatment as part of their treatment.

The 5-year PFS, OS and DSS figures were 52%, 60% and 71%, respectively. IPI correlated with survival, as expected. CNS progression was rare as in only twelve patients CNS progression was recorded as the first recurrence. IPI and Stage correlated with CNS recurrence risk.

The patients treated with R-chemo did not have longer survival than non-R treated patients. The R-chemo-treatment did not lead to lower risk of CNS recurrence either. Patients with high IPI, on the other hand, had longer disease-specific survival when treated with R-chemo as part of their therapy (5-y DSS 44% vs 14%, p=0.019).

CNS-directed *iv* chemotherapy, *iv* HD-MTX or *iv* cytarabine or combination of these was given to 76 (40%) patients. Fifty-one of them were treated also with R-chemo as part of their treatment and 25 without R. CNS-directed chemotherapy as part of the therapy was used equally often in both patient groups; 43% of R-chemo-treated patients and 36% of non-R treated (p=0.443) received CNS-directed *iv* chemotherapy. Patients treated with *iv* CNS-directed treatment as part of their treatment were younger than patients not treated with *iv* CNS-directed treatment (among patients treated with *iv* CNS-directed treatment 42% were under or 60 years and 58% were over 60 years whereas among patients not treated with *iv* CNS-directed treatment 16% of patients were under or 60 years and 84% were over 60 years). Otherwise, there were no significant differences in baseline characteristics in the different treatment groups.

Longer survival time was recorded for patients treated with *iv* CNS-directed treatment. The difference remained significant also when adjusted for age.

Forty-seven patients (42%) were treated with *it* CNS-directed treatment. This treatment was more commonly used in R-chemo-treated patients (42% vs 19%, p=0.014) and in Denmark (27% vs 7%, p<0.001). Also, 16 patients received both *iv* and *it* CNS-directed treatment. For R-chemo-treated patients, *it* CNS-directed treatment did not correlate with survival.

CNS progression as first relapse was recorded for twelve patients (6%). Eight of them were treated with *iv* CNS-directed treatment, one with *it* and *iv* CNS-directed treatment and none with only *it* CNS-directed treatment. There was no difference in CNS progression at first relapse between these treatment groups.

Seventy-five patients received radiotherapy for contralateral testis and for 13 patients the contralateral testis was surgically removed, thus the contralateral testis was treated in 88 patients (47%). There were no significant differences in patient characteristics between the patients for whom the contralateral testis was treated and for whom the contralateral testis was not treated. Nevertheless, the contralateral testis was more often treated in R-treated patients (53% vs 36%, p=0.035). Additionally *it* CNS-directed treatment was more common in the group of patients for whom the contralateral testicle was treated (65% vs 37%, p<0.001). Longer survival was recorded for patients receiving treatment for the contralateral testis (for patients receiving treatment for contralateral testis PFS 63%; OS 70%; and DSS 80%, whereas for patients not receiving treatment for contralateral testis PFS 43%, p=0.001; OS 51%, p=0.003; and DSS 63%, p=0.002, respectively).

In multivariate analysis, *iv* CNS-directed treatment, treatment of contralateral testis, age under 70y and low IPI significantly correlated with longer PFS and OS, whereas low IPI significantly correlated also with longer DSS. In multivariate analysis, low stage and low IPI score correlated with lower risk of CNS recurrence.

Lymphoma samples of 74 Finnish patients were collected. Fifty-six patients (76%) had non-GCB phenotype tumour according to Hans algorithm. Sixty patients with lymphoma tissue available were treated with (R)-CHOP like therapy and 46 (77%) had non-GCB DLBCL. Non-GCB phenotype was associated with inferior survival (5-y PFS 53% vs 87%, p=0.05).

Sixty (66%) of cases were positive for BCL2, which associated with shorter survival (5y PFS 64% vs 57%, p=0.112; 5y OS 49% vs 71%, p=0.047; 5y DSS 73% vs 90%, p=0.105). BCL6 was positive in 28 (31%) cases, but BCL6 positivity did not correlate with survival.

8.4 Lymphopenia in PT-DLBCL

Data of 178 patients with data on ALC and treated with CHOP or CHOP-like regimen was collected. At diagnosis the mean age was 67 years and median 69 years with an age range of 37 to 88 years. The median PFS and OS were 46 and 55 months, respectively. The median ALC at diagnosis was 1.385 $x10^9$/l with a range of 0.196 $x10^9$/l to 10.600 $x10^9$/l. Immunochemotherapy containing R was used for 109 patients. The patient characteristics among immunochemotherapy treated patients were similar to the patient characteristics in the total cohort of 178 patients. Among R-chemo-treated patients IPI and its parameters apart from age (PFS) and high LDH (OS) correlated with shorter survival.

Lymphopenia (ALC<1.3 $x10^9$/l) was found to be associated with known risk factors i.e. Ann Arbor >2, elevated LDH and IPI>2. CNS-directed treatment and R treatment were equally distributed among the subgroups of lymphopenic and non-lymphopenic patients.

ALC at diagnosis did not correlate with survival as continuous variable in Cox regression analyses for the entire cohort (PFS RR 0.870, 95% CI 0.685-1.105, p=0.254; OS RR 0.813, 95% CI 0.608-1.087, p=0.162). Still, among 109 patients treated with immunochemotherapy, a lower risk of progression was recorded for patients with higher ALC as continuous variable and a trend wise lower risk of death was also observed (PFS RR 0.506, 95% CI 0.324-0.790, p=0.003; OS RR 0.669, 95% CI 0.425-1.054, p=0.083).

Due to the leading role of immunochemotherapy today, further analyses were made with R-chemo-treated patients. In univariate analysis dichotomized ALC (ALC>1.3 $x10^9$/l vs ALC ≤ 1.3 $x10^9$/l) was recognized as a potential prognostic factor, and in multivariate analysis recorded as an independent prognostic factor. Among patients treated with R the results of univariate analysis (analyzed with Age >60, Stage 1-2, ECOG 0-1, LDH high, extranodal sites >1, IPI 0-2 and *iv* CNS-directed treatment) showed PFS RR 0.350, 95% CI 0.197-0.623, p<0.001; OS RR 0.491, 95% CI 0.265-0.909, p=0.024; and the results seen in multivariate analysis were PFS RR 0.514, 95% CI 0.279-0.946, p=0.033; OS RR 0.732, 95% CI 0.381-1.404, p=0.347. In Kaplan-Meier analyses lymphopenic R-treated patients had shorter PFS and OS rate than the non-lymphopenic R-treated patients (5-y PFS and 5-y OS for lymphopenic patients 31% and 47%, whereas 5-y PFS and 5-y OS for the non-lymphopenic 67%, p<0.001 and 68%, p=0.021). In addition, among the non-lymphopenic patients, the ones treated with R as part of their immunochemotherapy had longer survival than patients not treated with R as part of their treatment (R-treated non-lymphopenic 5-y PFS 67% and 5-y OS 68%, non-R-treated non-lymphopenic 5-y PFS 41%, p=0.005 and 5-y OS 57%, p=0.168). On the other hand, among lymphopenic patients a clear difference in survival was not recorded.

The benefit of CNS-directed treatment among R-treated patients was also studied. In uni- and multivariate analysis *iv* CNS-directed treatment associated with longer survival, as expected. Still, an association with improved survival was not recorded for lymphopenic patients treated with *iv* CNS-directed (PFS RR 0.645 95% CI 0.266-1.563, p=0.331; OS RR 0.355, 95% CI 0.120-1.045, p=0.060), but among non-lymphopenic

patients, association to longer PFS and OS was recorded (*iv* CNS dir treated; PFS RR 0.176 95% CI 0.046-0.665, p=0.010; OS RR 0.223 95% CI 0.058-0.862, p=0.030). In Kaplan-Meier analyses patients treated with *iv* CNS-directed chemotherapy had significantly longer survival among non-lymphopenic patients (PFS 89% vs 51%, p=0.004; OS 89% vs 53%, p=0.009), but not among lymphopenic patients (PFS 32% vs 31%, p=0.605; OS 61% vs 41%, p=0.140).

Among lymphopenic or non-lymphopenic patients treated with R, an association to survival was not found for patients treated with *it* CNS chemotherapy as compared to patients not treated with CNS directed treatment at all (among lymphopenic patients PFS RR 0.823, 95% CI 0.535-1.266, p=0.376; OS RR 0.740, 95% CI 0.463-1.181, p=0.207; among non-lymphopenic patients PFS RR 0.904 95% CI 0.553-1.479, p=0.688; OS RR 1.003, 95% CI 0.603-1.668, p=0.990).

8.4.1 AMC and LMR in PT-DLBCL

The impact of blood absolute monocyte count (AMC) was also tested as continuous variable. The clinical data of AMC was available for 156 patients, treated with or without R and with CHOP treatment or alike. Mean age of patients at diagnosis was 68 and median 70, with a range of 37 to 88 years, while median PFS and OS were 44 and 54 months, respectively. Median AMC was 0.520 $x10^9$/l, with a range of 0.100 $x10^9$/l to 1.680 $x10^9$/l.

In the subcohort of R-chemo-treated patients (n=95), mean age at diagnosis was 69 years and median 70 years with a range of 37 to 88 years, while median AMC was 0.530 $x10^9$/l with a range of 0.100 $x10^9$/l to 1.680 $x10^9$/l. The median PFS and OS were 45 and 52 months, respectively.

In the total cohort of 156 patients or in the subgroup of patients treated with R-chemo, a correlation with survival time was not recorded for AMC. LMR as continuous variable did not either correlate with survival time (PFS RR 0.918, 95% CI 0.813-1.036, p=0.164; OS RR 0.873, 95% CI 0.756-1.008, p=0.065). However, LMR correlated with longer survival time among patients treated with R (PFS RR 0.724, 95% CI 0.577-0.910, p=0.006; OS RR 0.776, 95% CI 0.610-0.986, p=0.038). The patients were divided into two groups for survival analyses by LMR using the earlier reported cut-off value of 3.0. In multivariate analysis in the total patient population with ALC and AMC available, LMR was not an independent prognostic factor, whereas among the 95 patients treated with R, LMR proved to have prognostic power (high LMR PFS RR 0.372, 95% CI 0.176-0.785, p=0.010; OS RR 0.400, 95% CI 0.175-0.915, p=0.030).

Eighty-five per cent of lymphopenic patients had low LMR, while 67% of non-lymphopenic patients had high LMR (p<0.001). R-chemo-treated patients with LMR<3 had shorter survival time in Kaplan-Meier analyses than patients with LMR≥3 (5-y PFS 38% vs 72%, p=0.003; 5-y OS 52% vs 74%, p=0.033).

9 Discussion

Two extranodal locations were selected, SNT and PT-DLBCL, to study their clinical behavior and biological features. The intention was to examine the impact of immunochemotherapy and CNS-directed chemotherapy on the outcome of the patients with extranodal DLBCL. CNS events were, however, rare at our institutions.

9.1 SNT DLBCL

As has been reported in NHLs in general, the incidence of SNT lymphomas and SNT DLBCL has increased during the studied period of time. The increasing incidence is partly explained by improved diagnostic, and longer life expectancy in the population. Acquired immunodeficiency syndrome (AIDS) increased the incidence of lymphomas in general (Aisenberg 2000). Nonetheless, incidence of HIV is low, 4.3/100 000 in the Helsinki and Uusimaa Hospital District (National Institute of Health and Welfare and Statistics Finland, 2017 data) and as only three of the tested SNT lymphoma patients were positive for HIV, HIV cannot explain the increase in incidence.

Baseline characteristics of the SNT DLBCL patients in the present study were similar to previously reported cohorts (Kanumuri et al., 2014, Dubal et al., 2015, Shohat et al., 2004, Abbondanzo, Wenig 1995, Cuadra-Garcia et al., 1999, Sandner et al., 2013). The incidences of the previous reports from USA have been 0.06-0.1/100 000, whereas in the present series the incidence for SNT DLBCL varied between 0.08 and 0.17/100 000 calculated in ten year periods (Kanumuri et al., 2014, Dubal et al., 2015).

Symptoms that could refer to common cold have been reported to occur in about half of the SNT lymphoma patients (Shohat et al., 2004, Quraishi et al., 2000, Peng et al., 2014). In the present series 60% of the patients had these symptoms and almost half of the patients had general symptoms. This is probably the reason, why the time from first symptoms to diagnosis was even 5 months in the present study.

It was hypothesized that paranasal DLBCL patients would have shorter survival, as they were thought to be more challenging location for diagnosis, but surprisingly survival did not correlate with anatomical location. However, the patients with paranasal DLBCL got more often CNS-directed chemotherapy as part of their treatment. Thus, more aggressive treatment could have overcome the worse prognosis in paranasal location.

In this cohort, SNT DLBCL had a different immunophenotype distribution from nodal DLBCL or DLBCL in Waldeyer's ring, and immunophenotype also varied according to SNT distribution. Overall, GCB phenotype was almost as frequent as non-GCB in the present series in paranasal location, but among all SNT cases, non-GCB was the most common. Different SNT locations have different bacterial microbiome, which also changes for instance with age (Proctor, Relman 2017, Hauser et al., 2016) and thus lymphomas arising at different locations have predisposed to different kinds of foreign antigens which may be postulated to predispose to different kinds of lymphomas. In addition, in paranasal sinuses the excretion remains longer time than in nasal

cavity or nasopharynx, which makes the environment different. Different kind of antigen exposure might explain some of the differences in immunophenotype in different SNT locations.

Tumours in different SNT locations were found rather evenly and commonly positive for BCL2 and BCL6. The immunohistochemical profile leads to assumption that SNT DLBCL could be high risk DLBCL, but due to small number of cases in the present study, differences in survival according to immunohistochemical profile could not be shown. Thus, GCB expression did not correlate with risk of progression. Likewise, BCL2 positivity did not correlate with higher risk of progression. However, earlier reports have found GCB expression to correlate with lower and BCL2 expression with higher risk of progression (Swerdlow et al., 2017, Sarkozy et al., 2015, Akyurek et al., 2012, Johnson et al., 2012). In lymphoma sample analysis of the present study, BCL6 expression did not correlated with risk of progression either. The prognostic significance of aforementioned immunohistologic factors should be studied in a larger, preferably prospective study, to gain more clear results.

The patients receiving R as part of their immunochemotherapy had longer PFS and OS than the patients treated without R. The results are consistent with earlier reported results of DLBCL in general (Coiffier et al., 2002, Habermann et al., 2006, Pfreundschuh et al., 2008, Pfreundschuh et al., 2006).

Even though Schmitz et al. reported SNT location not to associate with increased risk of CNS progression (Schmitz et al., 2016), to our knowledge, it has not been shown previously that CNS-directed chemotherapy would not benefit the patients with SNT DLBCL patients. As only one patient had CNS progression in the present series, the impact of R or CNS-directed therapy on CNS progression could not be evaluated. Nevertheless, the patients treated with CNS-directed therapy as part of their chemotherapy had longer PFS and OS than the patients not receiving CNS-directed therapy. In addition, the longest PFS and OS was recorded in patients treated with both R and CNS-directed chemotherapy. The results of the present study thus suggest that the addition of R and CNS-directed chemotherapy to conventional CHOP can result in a better systemic control of the disease and thus longer survival.

9.2 PT-DLBCL

This study showed the incidence of PT-DLBCL has increased over the studied period of time, as has been reported in NHLs in general. Like in SNT-DLBCL, this is explained by longer life expectancy and improved diagnostics. None of the tested PT-DLBCL patients were positive for HIV.

In the present study, the proportion of non-GCB in PT-DLBCL defined by immunohistochemistry was similar to earlier reported, as well as survival and age distribution of the patients (Deng et al., 2016, Li et al., 2010). Even immunohistochemically determined, the patients with non-GCB PT-DLBCL had shorter survival than

GCB PT-DLBCL patients. A clear difference in survival according to BCL2 or BCL6 positivity was not observed.

The impact of the addition of R to chemotherapy in PT-DLBCL has been controversial in previous retrospective series (Gundrum et al., 2009, Kridel et al., 2017, Mazloom et al., 2010). In a prospective trial Vitolo et al. found that immunochemotherapy resulted in longer survival compared to historic cohort treated without R (Vitolo et al., 2011). Patients with high IPI and treated with R as part of their chemotherapy had longer survival than the patients with high IPI and not receiving R in the present study, as has also been reported previously (Kridel et al., 2017). However, in the total PT-DLBCL study cohort a difference in survival was not observed when comparing the patients receiving R as part of their therapy with the patients not receiving R. The rather small number of the patients in the present series might restrict the ability to note small differences in survival.

Addition of R to chemotherapy did not lead to lower number of CNS events, a finding that has also been reported earlier (Boehme et al., 2009, Schmitz et al., 2012, Kridel et al., 2017, Deng et al., 2013). The patients receiving *iv* CNS-directed chemotherapy as part of their chemotherapy did not either have lower CNS progression rate compared to patients not treated with *iv* CNS-directed chemotherapy. However, patients who relapsed and were unfit for additional chemotherapy might not have gone through comprehensive diagnostic procedures at the time of relapse, i.e. a true CNS relapse might have not been observed. This effect, however, should be similar in all treatment groups.

The patients treated with *iv* CNS-directed therapy had better OS and PFS even though there was no difference in CNS progression rate. Therefore, the results of the present study suggest that the addition of *iv* CNS-directed therapy to R-CHOP improves the systemic control of PT-DLBCL. However, the conclusion should be confirmed in prospective clinical trials.

Even though patient characteristics were equally distributed between different treatment groups, there might have been selection bias considering the retrospective nature of the study. The patients treated with *iv* CNS-directed treatment were younger than the other patients. Nevertheless, older patients treated with *iv* CNS-directed treatment had similar survival as younger ones treated with *iv* CNS-directed treatment, and the prognostic impact of *iv* CNS-directed treatment was independent of age (age <70) in multivariate analysis.

Treatment with *it* CNS-directed treatment did not lead to longer survival, which had been reported already earlier by others (Zucca et al., 2003, Chua et al., 2002).

The testes are considered to be an immunopriviledged site surrounded by blood-testis barrier that protects the germ cells from eradication by the immune system (Fijak et al., 2011). DLBCL arising in testis often relapse in other extranodal locations, especially in contralateral testis or the CNS that is protected by blood-brain barrier (Zucca et al., 2003, Fonseca et al., 2000, Tondini et al., 1999, Seymour et al., 2001). To prevent

chemotherapy evasion of lymphoma cells in the similar immunopriviledged compartment of the contralateral testis and thus recurrence, it has been recommended to treat the contralateral testis either with radiotherapy or orchiectomy (Vitolo et al., 2016, Conrad, Go 2009). Even though treatment of contralateral testis has not been specifically studied in prospective trials, in retrospective series prophylactic treatment of contralateral testis has been associated with reducted number of relapses in contralateral testis and longer overall survival (Tokiya et al., 2017, Ho et al., 2017). A longer survival for the patients receiving prophylactic treatment for contralateral testis was observed. The effect was independent of used (immuno)chemotherapy and known risk factors.

Lymphopenia has been shown to associate with shorter survival in patients with primary DLBCL. Indeed, lymphopenia is a sign of general immunodeficiency. Earlier studies have found lymphopenia to be independent prognostic factor in general in DLBCL (Porrata et al., 2012, Porrata et al., 2010, Vaidya, Witzig 2014) and according to the results of the present study, this applies also in R-treated PT-DLBCL patients.

As described above (5.5.5 Immunohistochemical algorithms), aberrant or reduced expression of MHC I and MHC II molecules that are important in antigen presentation and lymphocyte activation, correlates with inferior survival in DLBCL. Patients with DLBCL, having tumour microenvironment inflamed with a high number of T-cells, had a better response to rituximab-based immunochemotherapy in a recent publication from our group (Leivonen et al., 2018). Also a vaccinal effect of R has been proposed, where lymphocytes would also have an important role (Cartron et al., 2004). Taken together, immunologic mechanisms are important not only in lymphomagenesis, but also in the treatment of lymphoma. In the present study, lymphopenic patients did not benefit of the addition of R to the chemotherapy compared with lymphopenic patients treated with chemotherapy without R. On the contrary, non-lymphopenic patients benefitted of the addition of R to the chemotherapy as compared with non-lymphopenic patients treated with chemotherapy without R. According to the current results, normal counts of lymphocytes in blood is needed to make the action of immunochemotherapy possible.

In the analyses on ALC, the lower limit of normal absolute lymphocyte count in peripheral blood was used as cut-off value. This cut-off value should therefore be considered as indicative for other studies. Earlier studies on DLBCL in general have used varying cut-off values. Altogether, the results rather reflect the negative prognostic value of low lymphocyte count compared to high lymphocyte count, when compared to one another.

Non-lymphopenic patients treated with immunochemotherapy benefitted of the addition of *iv* CNS-directed treatment to their immunochemotherapy, whereas among lymphopenic patients a clear benefit of the addition of *iv* CNS-directed treatment was not seen.

The present study highlights the need to find new treatment-options for PT-DLBCL, especially for lymphopenic patients. Further efforts should be made to find an alternative for R, especially lymphopenic patients would need new treatment strategies.

Although this study did not identify AMC as a prognostic factor in PT-DLBCL, LMR was recorded as an independent prognostic factor for PFS and OS among patients treated with immunochemotherapy. Even though according to the data of the current publication, LMR seems to be largely derivative of ALC, not all lymphopenic patients had low LMR and not all non-lymphopenic patients had high LMR. Therefore, also the benefit of using LMR in testicular DLBCL patients should be studied in prospective studies.

10 Future perspectives

New prognostic markers are needed and treatments should be addressed according to risk factors for patients with extranodal lymphoma. PT-DLBCL patients with high IPI and PT-DLBCL patients that were not lymphopenic, were found to benefit from the addition of R to chemotherapy. Additionally, CNS-directed chemotherapy was found to associate with longer survival in SNT-DLBCL and *iv* CNS-directed chemotherapy was found to associate with longer survival in PT-DLBCL. However, in lymphopenic patients with PT-DLBCL, no improvement in survival was seen. The results should be confirmed in prospective clinical trials.

PD-1 check point inhibitor could be one possible new treatment strategy for PT-DLBCL, as PD-1 ligands are overexpressed in PT-DLBCL (Chapuy et al., 2016, Pollari et al., 2018). In addition, in a small patient series, PD-1 check point inhibitor was shown to have therapeutic efficacy in patients with primary CNS lymphoma and PT-DLBCL with CNS relapse (Nayak et al., 2017).

CAR-T treatment is under intensive research, and already used in relapsed DLBCL. A response rate of even 82% has been reported for patients with refractory DLBCL and treated with CAR-T treatment (Neelapu et al., 2017). CAR-T treatment has changed the treatment strategy for relapsed DLBCL patients, and is recommended for patients with relapse after second line treatment for WHO 0-1 patients (https://www.onkologiayhdistys.fi).

As DLBCL is a heterogenous disease, more personalized treatment strategies are needed. Chapuy et al. could discriminate a low risk ABC-DLBCL group and divide GCB-DLBCL into two groups with different outcomes (Chapuy et al., 2018). Schmitz et al. reported about four different genetic subtypes of DLBCL with different response to immunochemotherapy (Schmitz et al., 2018). A new genetic division of DLBCL is emerging. The classification of DLBCL will probably change as our knowledge of the disease genetics increases and treatments are studied separately in each genetic subtype.

11 Summary and conclusions

This study revealed

1) The slowly increasing incidence of SNT lymphomas in Northern European population, increasing incidence of SNT DLBCL and the distribution of SNT lymphomas in different locations
2) Immunophenotypic profile of SNT DLBCL, the frequency of BCL2 and BCL6 positivity, and the longer survival of patients treated with R-containing immunochemotherapy and CNS-directed chemotherapy in SNT DLBCL
3) The benefit of *iv* CNS-directed chemotherapy in PT-DLBCL and the benefit of addition of R to chemotherapy in certain subgroups and the significance of treating contralateral testis
4) Significance of ALC as prognostic factor for survival in immunochemotherapy treated patients with PT-DLBCL, and the benefit of addition of R and *iv* CNS-directed treatment in non-lymphopenic patients with PT-DLBCL. AMC did not have prognostic impact on survival in patients with PT-DLBCL

The incidence of both SNT and PT-DLBCL is slowly increasing. This study showed that both the addition of R to chemotherapy and CNS-directed treatment benefit the patients with SNT DLBCL, especially when used in combination.

The patients with PT-DLBCL benefitted from *iv* CNS-directed therapy and treatment of contralateral testis. In addition, non-lymphopenic and high risk patients with PT-DLBCL seemed to benefit from the addition of R to chemotherapy, whereas no clear benefit was seen among lymphopenic and low risk patients. In the future, we need to find more effective treatments for lymphopenic PT-DLBCL patients, possibly an alternative for R.

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